Imperial College London

Reproductive Medicine

Genesis of aneuploidy

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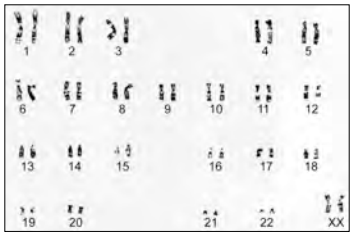
Human karyotype

- 46 chromosomes
- 22 pairs of autosomes
- 1 pair of sex chromosomes
- Notation:
  - Diploid: 46XX or 46XY
  - Monosomy X: 45X
  - Klinefelters: 47XXY



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Aneuploidy

The wrong number of chromosomes

- Triploidy (3 copies of every chromosome)
- Haploidy (1 copy of every chromosome)
- Aneuploidy
  - trisomy (3 copies of a specific chromosome)
  - monosomy (1 copy of a specific chromosome)

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Aneuploidy

- 35% of miscarriages are aneuploid
- Leading cause of pregnancy loss
- 0.3% newborns have a chromosomal abnormality
- Results in physical and mental disability

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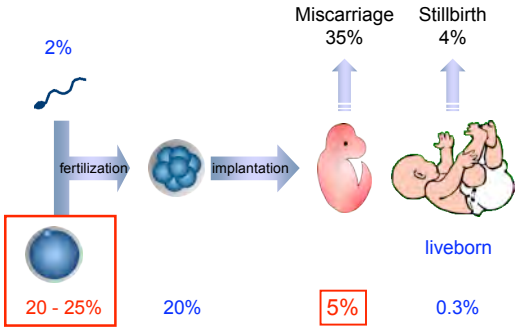
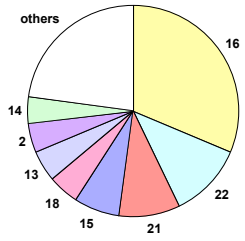
Oocyte: main source of aneuploidy



Frequency of different trisomies in clinical pregancies

- Monosomies do not survive
- Trisomy 16 most common, almost always lost early in development
- Trisomy 1 never observed



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Aneuploidies which survive to birth

Surviving trisomies

- Trisomy 21 (Down Syndrome) - 1/800 births
- Trisomy 13 - 1/20,000 births
- Trisomy 18 - 1/10,000 births

Surviving monosomies

- Turner Syndrome - (monosomy X)

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Incidence of aneuploidy during development

Gestation (weeks)			0	6-20	24-40	~40
				Mis-carriage	Stillbirths	Livebirths
Incidence	1-2%	~20%	~20%	35%	4%	0.3%
Most common aneu-ploidies	Various	Various	Various	45X* +16 +21 } 50% +22	+13 +18 +21	+13 +18 +21 XXX XXY XYY
*no other monosomies						

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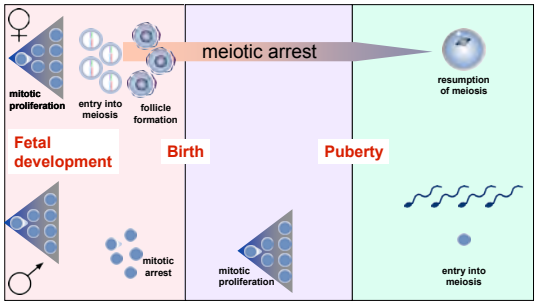
Tempo of meiosis different in males and females



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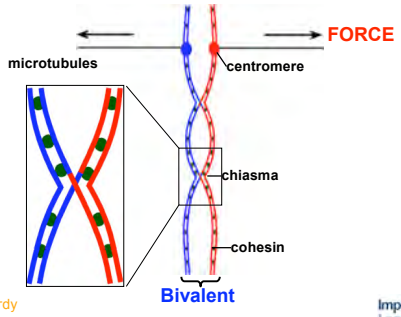
Chiasmata and cohesins essential for congression - establishing metaphase plate



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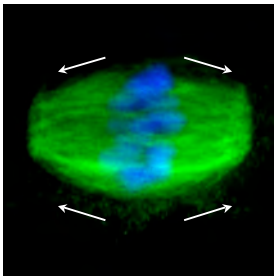
Congression

Microtubules move around seeking centromeres to attach to Bivalents 'jockey' for position – oscillating to-and-fro until all attached to 2 opposing microtubules and aligned on metaphase plate

mouse metaphase I spindle



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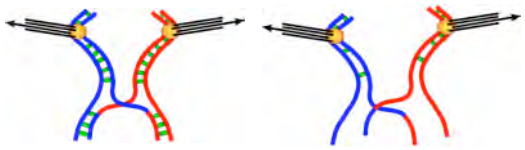
Homologue separation requires cohesin loss along arms…..



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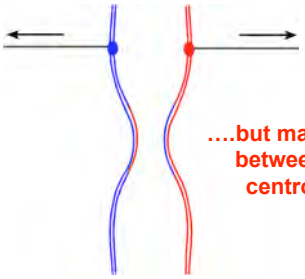
Homologue separation requires cohesin loss along arms…..



….but maintenance between sister centromeres

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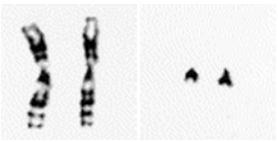
Chromosome size and crossing-over

- Chromosomes differ greatly in size
- Big chromosomes have more chiasmata
- Small ones have fewer chiasmata, and higher chance of none, ie being achiasmate
- Aneuploidy of small chromosomes more common



1 21

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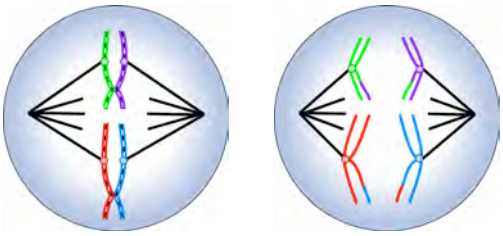
Normal meiosis I



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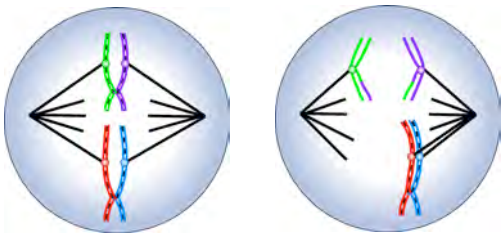
True non-disjunction; Meiosis I



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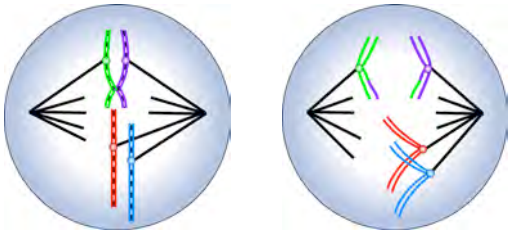
‘Achiasmate’ non-disjunction; Meiosis I



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Recombination and non-disjunction

- Chiasmata essential for keeping homologues together and stabilizing bivalent on meiotic spindle
- Stable bivalent allows capture of microtubules from opposite poles, so balanced segregation of homologues occurs
- Absence of chiasmata, or badly placed chiasmata can lead to non-disjunction
- e.g. 40% of maternal MI trisomy 21 cases result from achiasmate bivalent (ie no recombination)
- Sex chromosome trisomy usually paternal in origin - associated with failure of recombination in XY bivalent

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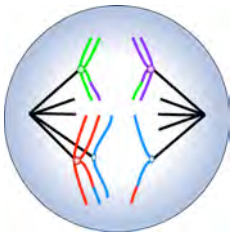
Premature separation of sister chromatids; Meiosis I



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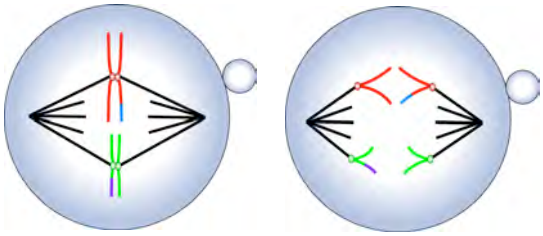
Normal Meiosis II



NB: occurs AFTER fertilization

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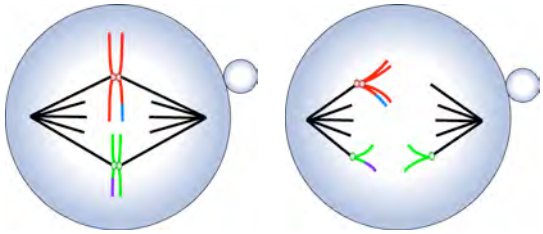
Meiotic non-disjunction: Meiosis II



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Post-zygotic non-disjunction

- Aneuploidy can also arise after fertilization, while the embryo is cleaving
- This gives rise to 'mosaic' embryos with mixtures of diploid, monosomic and trisomic cells
- The fate of the abnormal cells is unknown
  - apoptosis?
  - slower cleavage, so normal cells eventually predominate?

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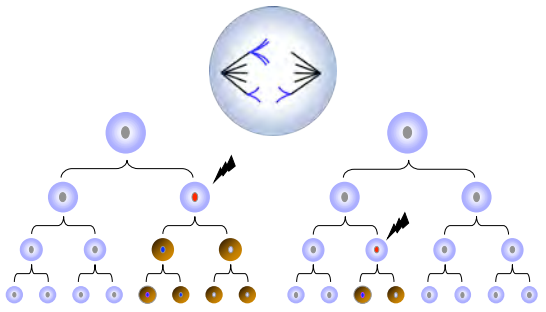
Mitotic non-disjunction



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Different chromosomes have varying sperm/oocyte, MI/MII, origins of trisomy

	Paternal		Maternal		
Trisomy	MI	MII	MI	MII	Mitotic*
2	28	–	54	13	6
7	–	–	17	26	57
16	–	–	100	–	–
18	–	–	33	56	11
21	3	–	65	23	3
XXY	46	–	38	14	3
XXX	–	6	60	16	18

numbers are % within row
* post zygotic

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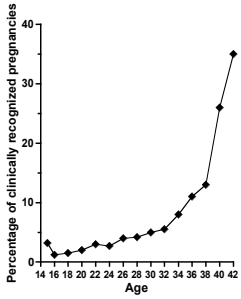
Aneuploidy and age



No effect of
- race
- geography
- socio-economic status

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Why does aneuploidy increase with age?

Relaxed selection hypothesis
- Reduced selection against trisomies?
  - uterus less able to recognize abnormal pregnancy
  - now not thought to be the case

Limited pool hypothesis
- Age effect might be due to scarcity of oocytes at optimal stages of maturation
- Mothers of Down syndrome individuals more likely to have reduced ovarian complement of eggs (either by surgery or congenital absence of one ovary)

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Why does aneuploidy increase with age?

Local factors hypothesis
- Breakdown of meiotic apparatus (spindle)?
  - spindles and chromosome alignment more abnormal in oocytes from older women (Battaglia, 1996; Volarcik, 1998)
- Prolonged exposure to environmental toxins?
- Increasing FSH levels in older women?
- Compromised circulation around growing follicles? Hypoxic oocytes prone to aneuploidy

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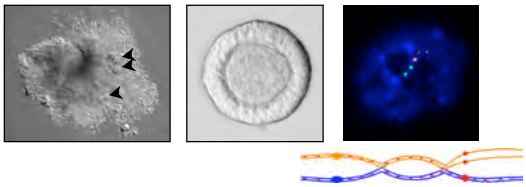
Why does aneuploidy increase with age?

- Degeneration of cohesins between chromatids in oocytes arrested for many decades?
  - could predispose oocyte to non-disjunction as chiasmata alone cannot hold bivalent together



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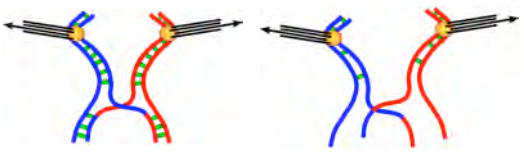
Chiasmata cannot hold homologues together without cohesion

During congression:



Result: Non-disjunction

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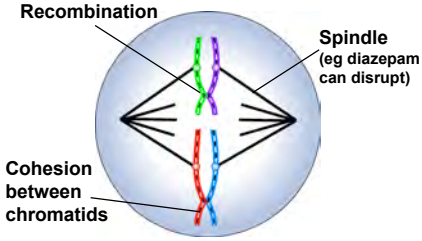
Key meiotic processes which, when disrupted, predispose oocyte to aneuploidy



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