

Nondisjunction

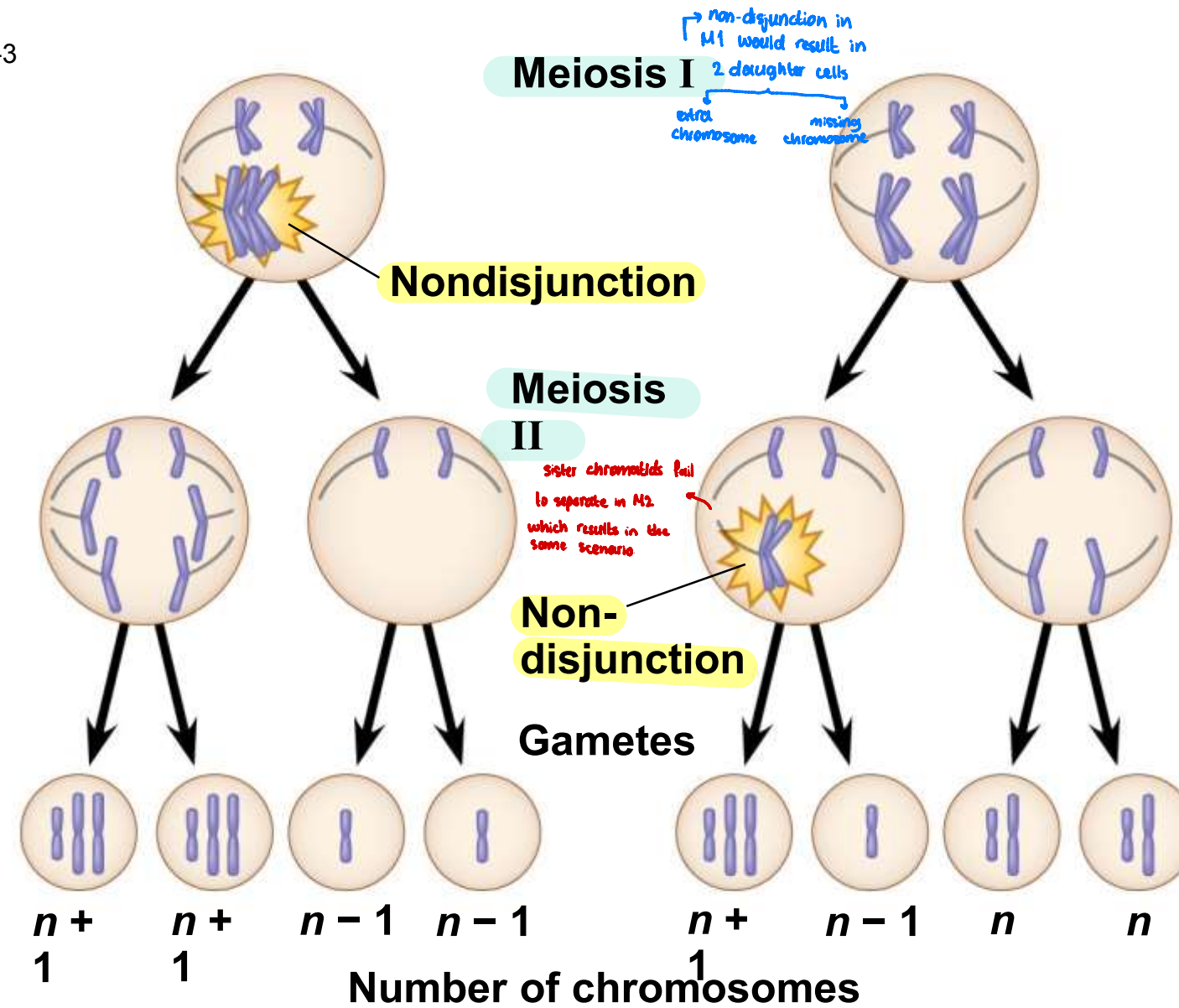
Failure of:

- (1) chromosome pair to disjoin during M1 or**
- (2) chromatids to separate in MII or mitosis.**

Abnormal Chromosome Number

- In **nondisjunction**, pairs of homologous chromosomes do not separate normally during meiosis
- As a result, one gamete receives two of the same type of chromosome, and another gamete receives no copy

Figure 15.13-3



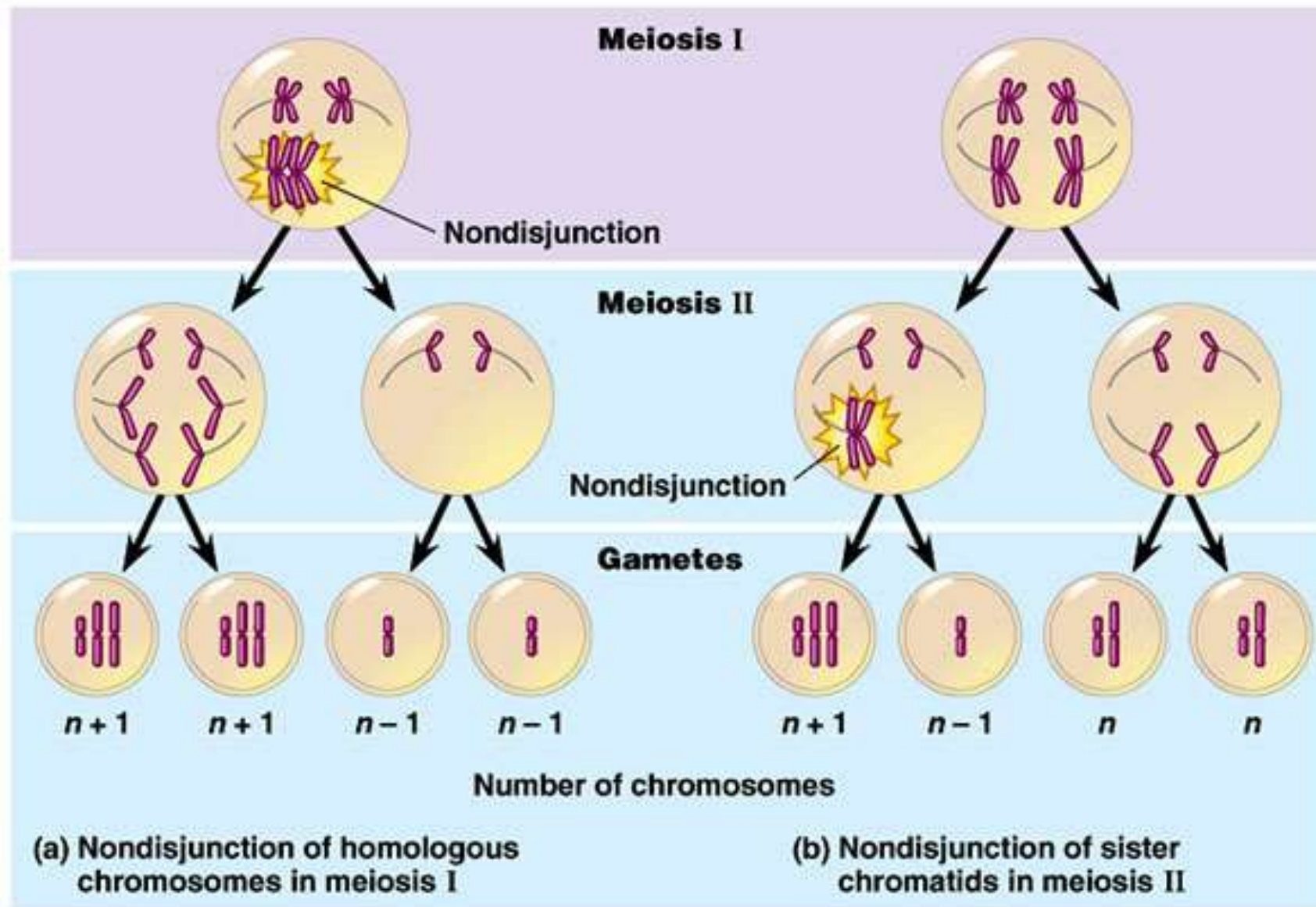
(a) Nondisjunction of homologous chromosomes in meiosis I

(b) Nondisjunction of sister chromatids in meiosis II


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* if non-disjunction happens during

- Meiosis 1: All daughter cells will have abnormal chromosome #.
 - 1/2 of them with an extra chromosome ($n+1$)
 - " " " missing chromosome ($n-1$)
- Meiosis 2:
 - 50% of daughter cells with normal # (n)
 - 25% with an extra chromosome ($n+1$)
 - 25% with a missing chromosome ($n-1$)



-
- extra or missing chromosome
which leads to a non-exact
multiple of n. **Aneuploidy** results from the fertilization of gametes in which nondisjunction occurred
 - Offspring with this condition have an abnormal number of a particular chromosome

- 
- A **monosomic** zygote has only one copy of a particular chromosome
 - A **trisomic** zygote has three copies of a particular chromosome

Trisomy

Additional (3 rather than 2) chromosome.

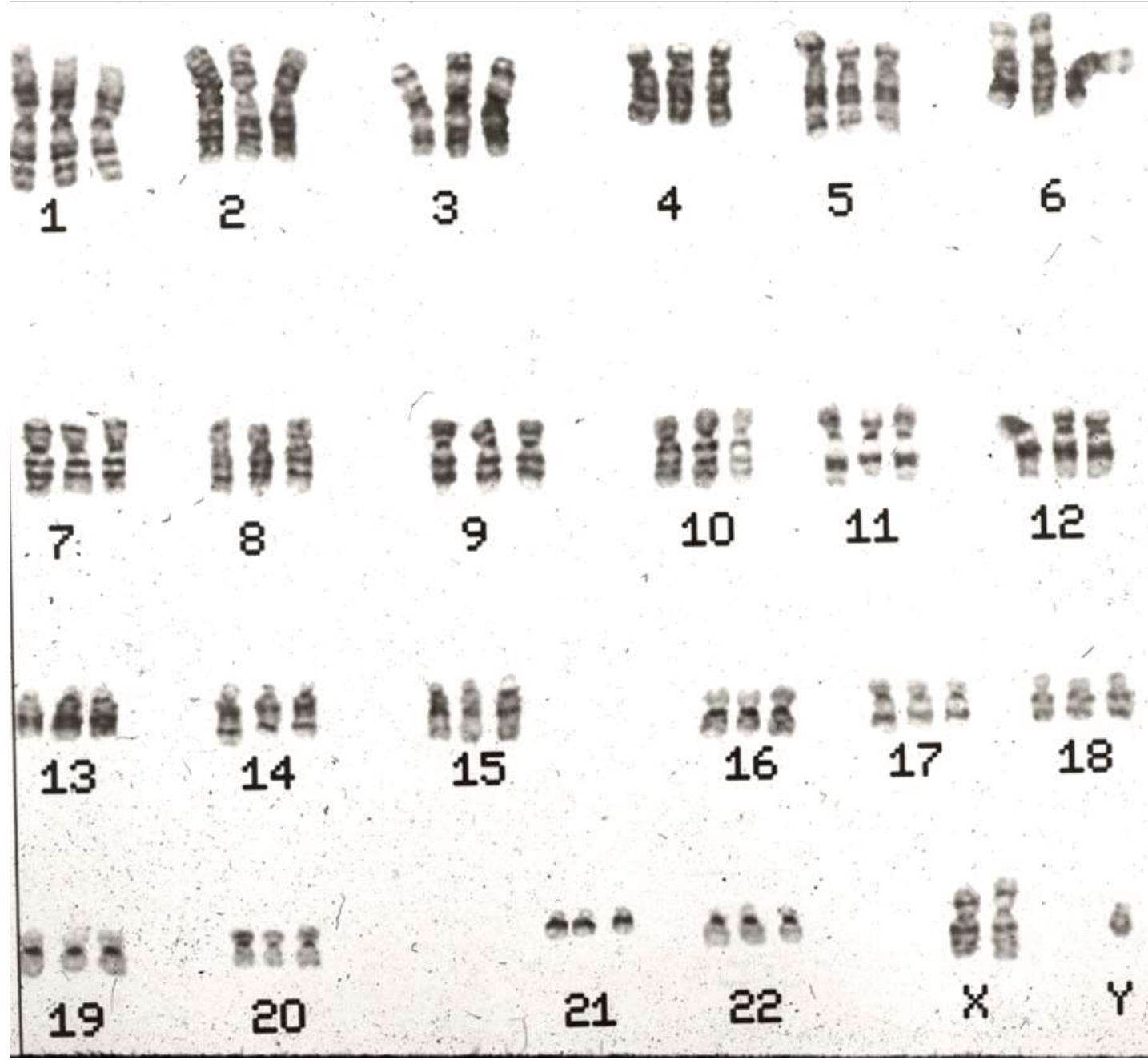
Monosomy

One chromosome of a pair missing.

- **Polyploidy** is a condition in which an organism has more than two complete sets of chromosomes
 - Triploidy ($3n$) is three sets of chromosomes \Rightarrow different from trisomy (aneuploidy)
 - \rightarrow multiples of n
 - \leftarrow triploid is an euploid
 - Tetraploidy ($4n$) is four sets of chromosomes
- Polyploidy is common in plants, but not animals
- Polyploids are more normal in appearance than aneuploids

Euploid - any chromosome number that is an exact multiple of the number of chromosomes in a normal haploid gamete (n). Most somatic cells are diploid (2N).

haploid (1 set), diploid (2 sets), triploid (3 sets), tetraploid (4 sets)



**Triploid
y
69,XXY**

Alterations of Chromosome Structure

** here, the # of chromosomes is unaffected.*

- Breakage of a chromosome can lead to four types of changes in chromosome structure
 - **Deletion** removes a chromosomal segment
 - **Duplication** repeats a segment
 - **Inversion** reverses orientation of a segment within a chromosome
 - **Translocation** moves a segment from one chromosome to another

Figure 15.14a

(a) Deletion



A deletion removes a chromosomal segment.



(b) Duplication

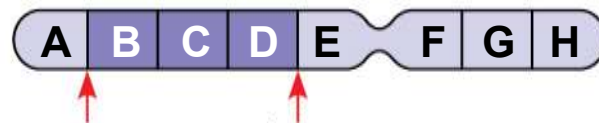


A duplication repeats a segment.



Figure 15.14b

(c) Inversion



An inversion reverses a segment within a chromosome.



(d) Translocation ⇒ i.e. between ch.9 & ch.22 which causes CML (Philadelphia)



A translocation moves a segment from one chromosome to a nonhomologous chromosome.



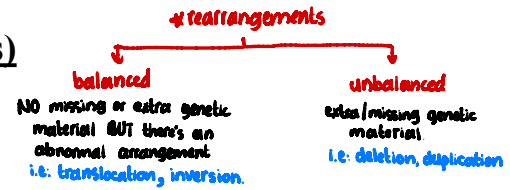
Unlike recombination which is a normal process where 2 non-sister chromatids of homologous chromosomes exchange genetic material in prophase I.

Human Disorders Due to Chromosomal Alterations

- Alterations of chromosome number and structure are associated with some serious disorders
- Some types of aneuploidy appear to upset the genetic balance less than others, resulting in individuals surviving to birth and beyond
- These surviving individuals have a set of symptoms, or syndrome, characteristic of the type of aneuploidy

Incidence of Chromosomal Abnormalities in Newborns

Type of Abnormality	Prevalence at Birth
Sex Chromosome Aneuploidy <small>* Aneuploidy could occur in autosomes or sex chromosomes.</small>	
Males (43,612 newborns)	
<small>ch. Y = male regardless of # of ch. X</small> 47,XXY <small>→ extra X chromosome (Klinefelter syndrome)</small>	1/1000
47,XYY	1/1000
Females (24,547 newborns)	
45,X	1/5000
47,XXX	1/1000
Autosomal Aneuploidy (68,159 newborns)	
Trisomy 21 <small>→ Down Syndrome (47 chromosomes)</small>	1/800
Trisomy 18	1/6000
Trisomy 13	1/10,000
Structural Abnormalities (68,159 newborns) (Sex chromosomes and autosomes)	
Balanced rearrangements	
Robertsonian	1/1000
Other (reciprocal and others)	1/885
Unbalanced rearrangements	1/17,000
All Chromosome Abnormalities	
Autosomal disorders and unbalanced rearrangements	1/230
Balanced rearrangements	1/500
Total	1/154



Data from Hsu LYF (1998) Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A (ed.), *Genetic Disorders and the Fetus*, 4th edition, Johns Hopkins University Press, Baltimore, pp. 179-248.

Down Syndrome (Trisomy 21)

- **Down syndrome** is an **aneuploid condition** that results from **three copies of chromosome 21** → this occurs due to non-disjunction during oogenesis.
- It affects about one out of every 700 children born in the United States
- **The frequency of Down syndrome increases with the age of the mother**, a correlation that has not been explained → there's a higher rate of non-disjunction during oogenesis in advanced maternal age.

EXPONENTIAL

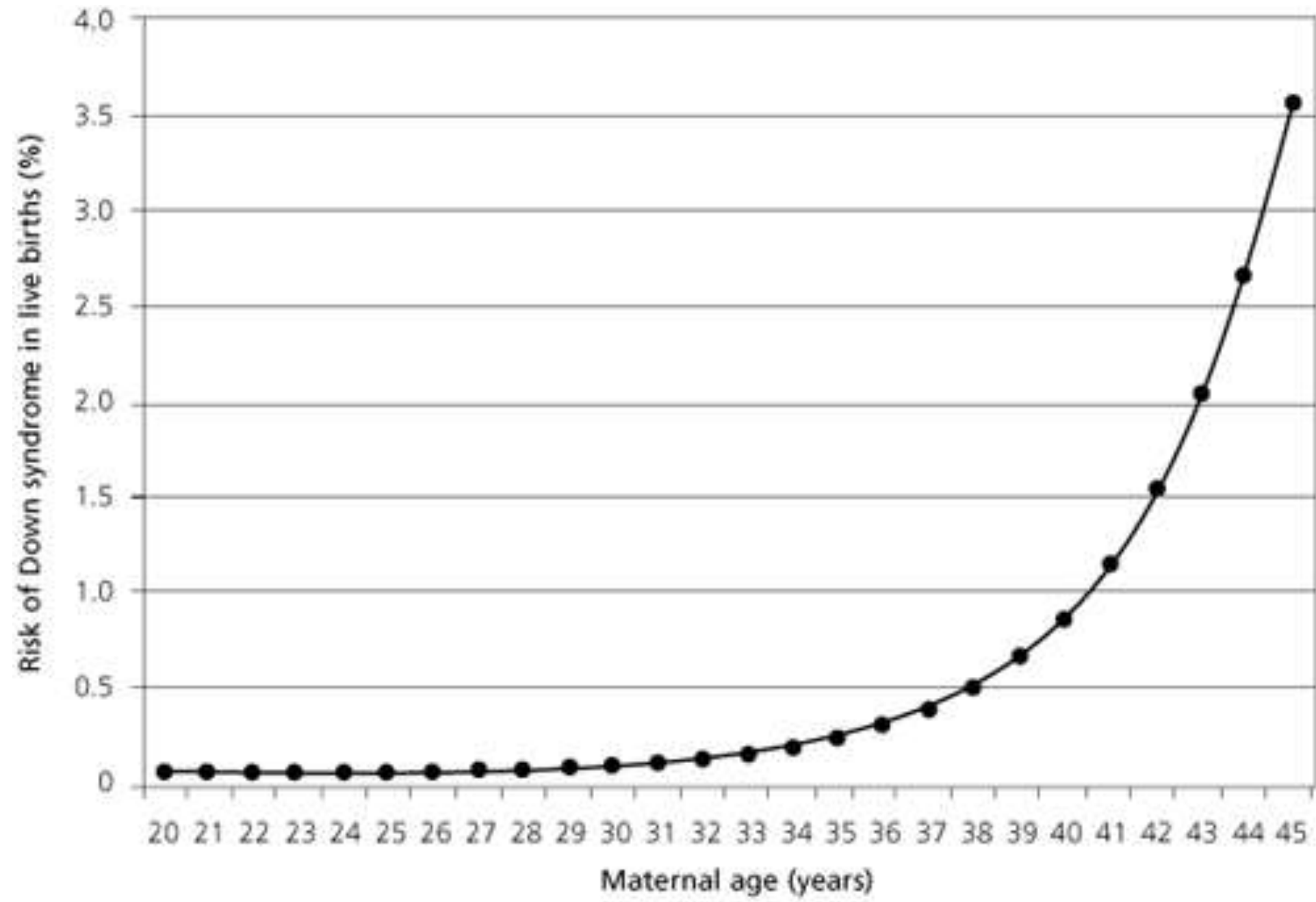
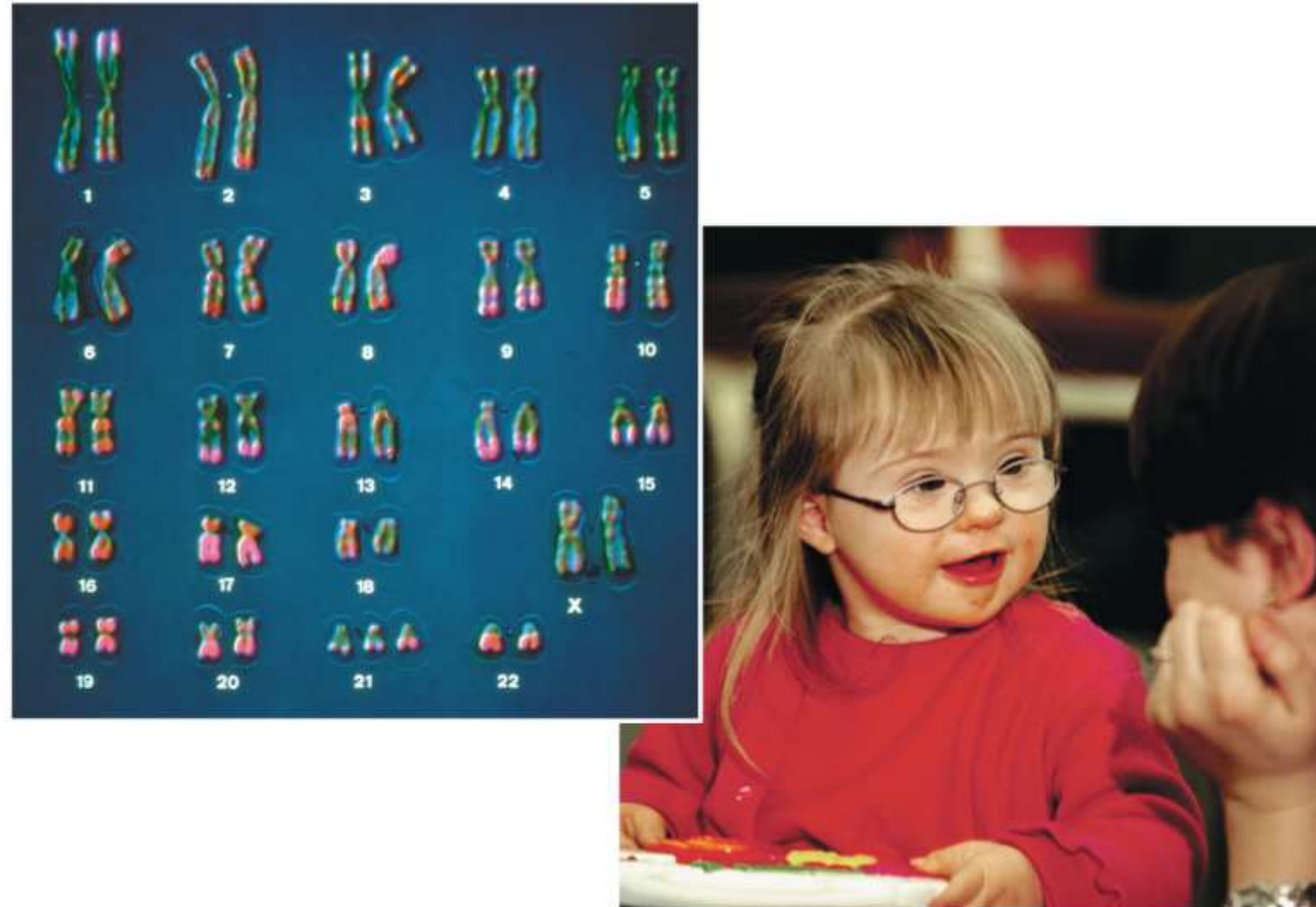
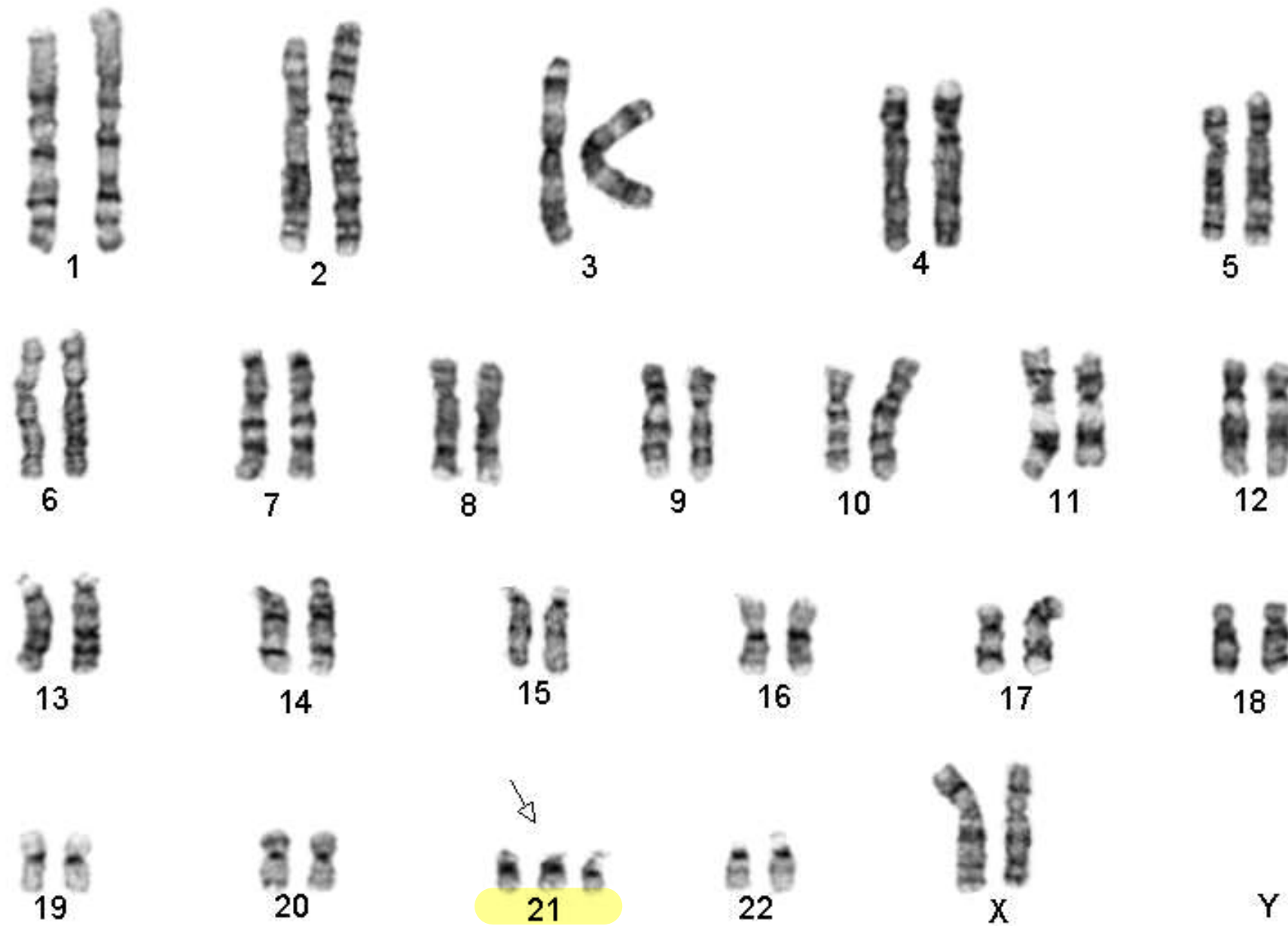
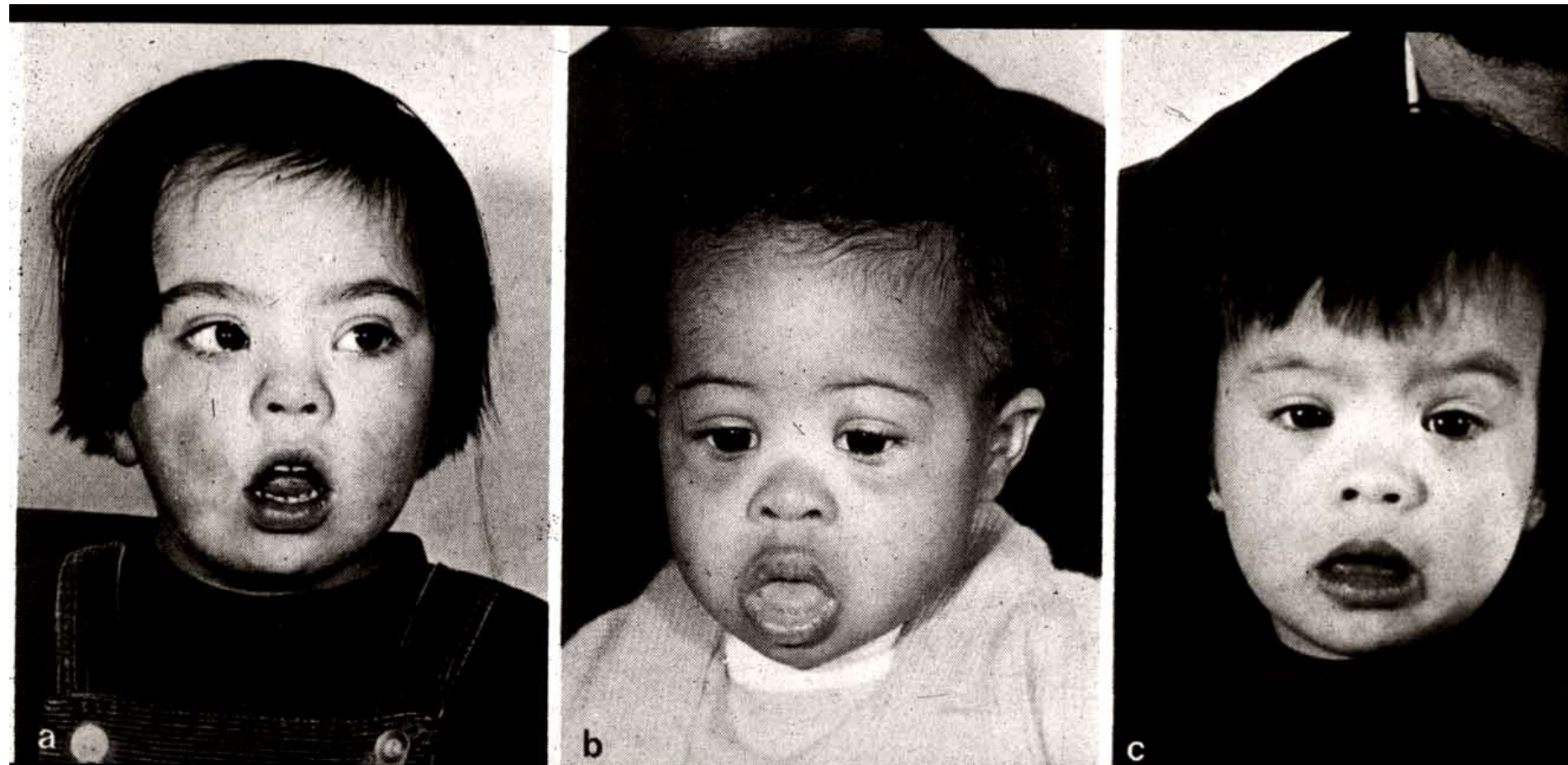


Figure 15.15



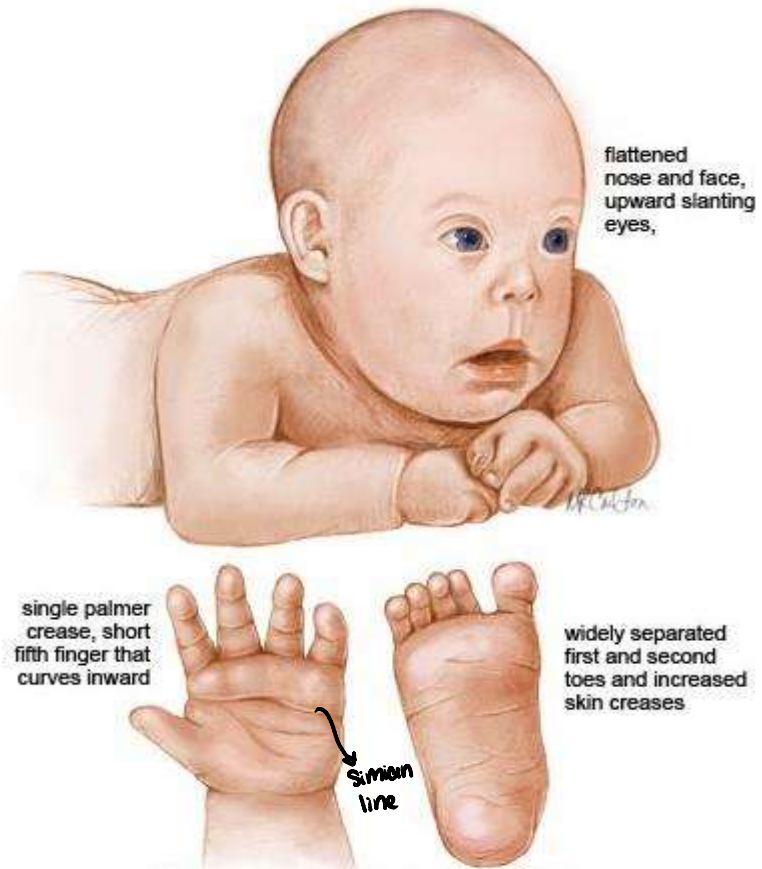
Most common numerical abnormality in liveborns is Trisomy 21 (Down syndrome)





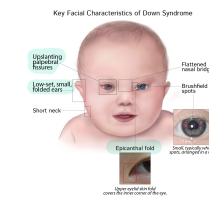
Male:Female Ratio - 3:2

Down Syndrome



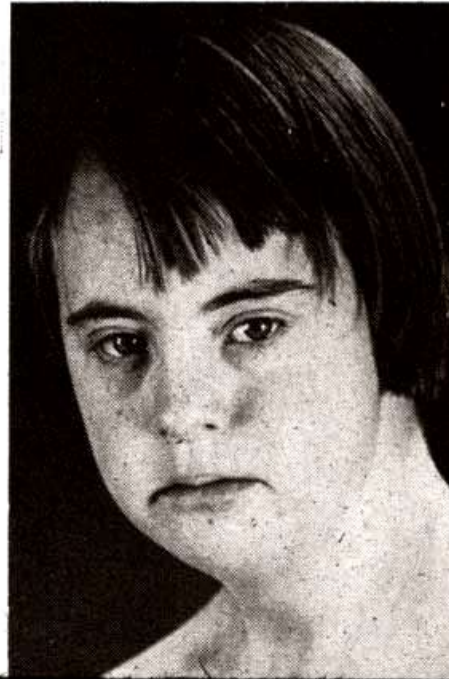
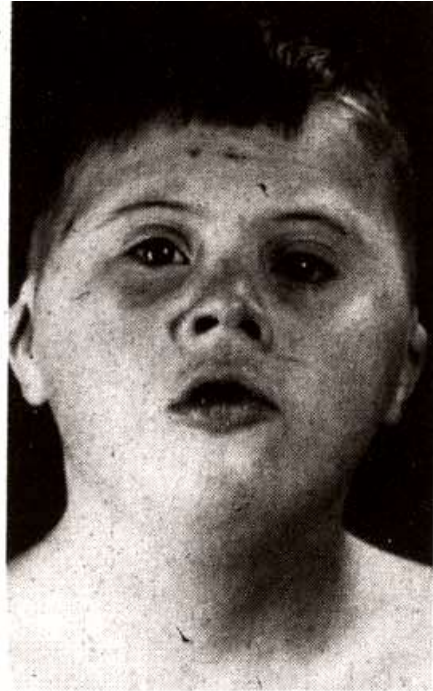
- Mental retardation (IQ 25-50) → *intellectual disability*
- *Low nasal bridge (90%)
- *Hypotonia (80%) ↓ *muscle tone, weakness*
- *Up slanting palpebral fissures (80%)
- Small, low-set ears (60%) *below normal position*
- *Congenital heart disease (30%-50%)*

- *Epicanthic folds
- Protruding tongue
- Intestinal problems
- Gap between first and second toes
- 15-fold increase in risk for leukemia
- *Simian line (transverse crease) (45%)



**These features are easily recognized at birth.*

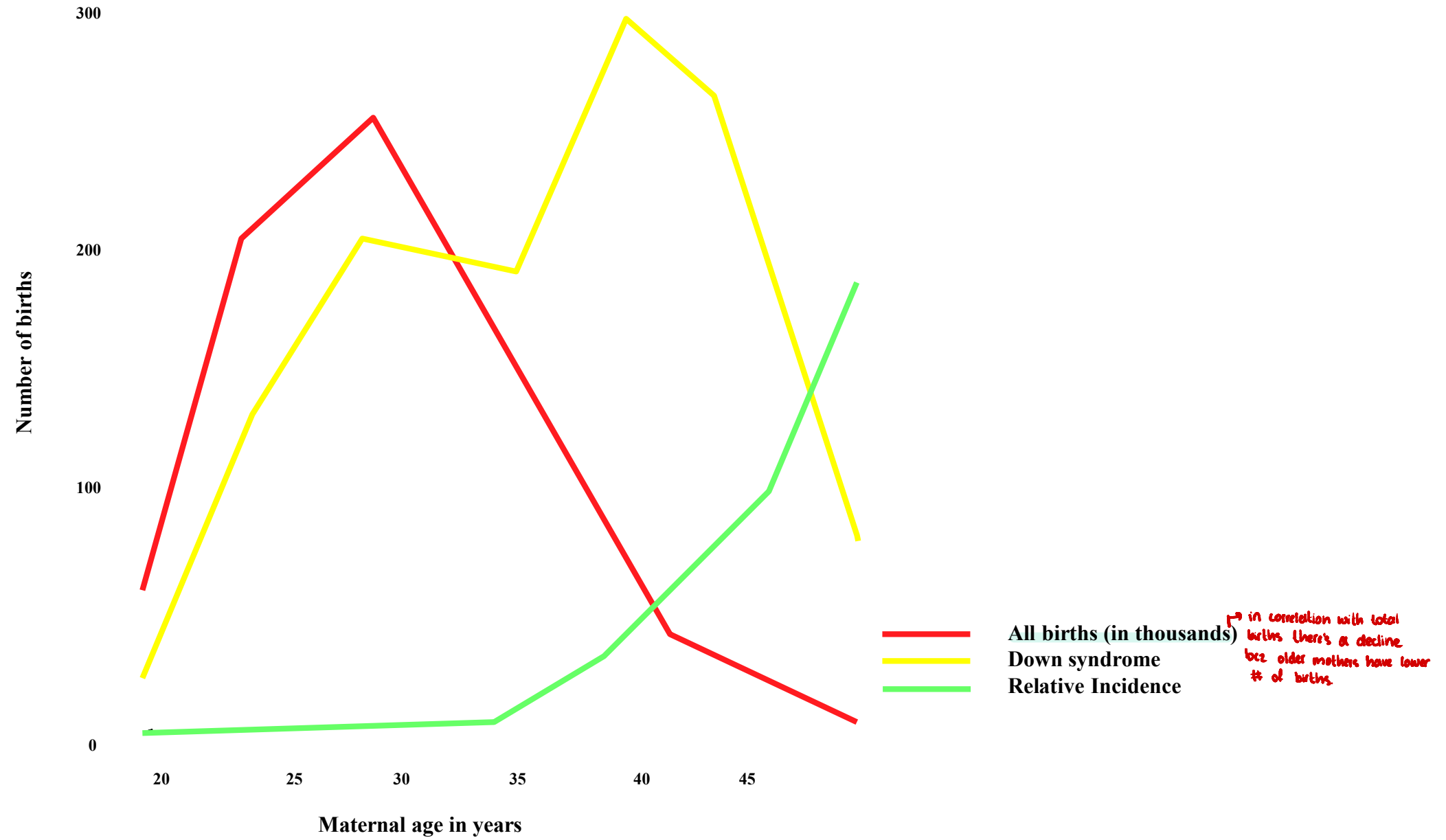
**The congenital heart problems noted in people having Down syndrome include ventricular septal defect (VSD) and arterioventricular defects (AV) canal. Approximately 40% with congenital heart disease die during the first year.

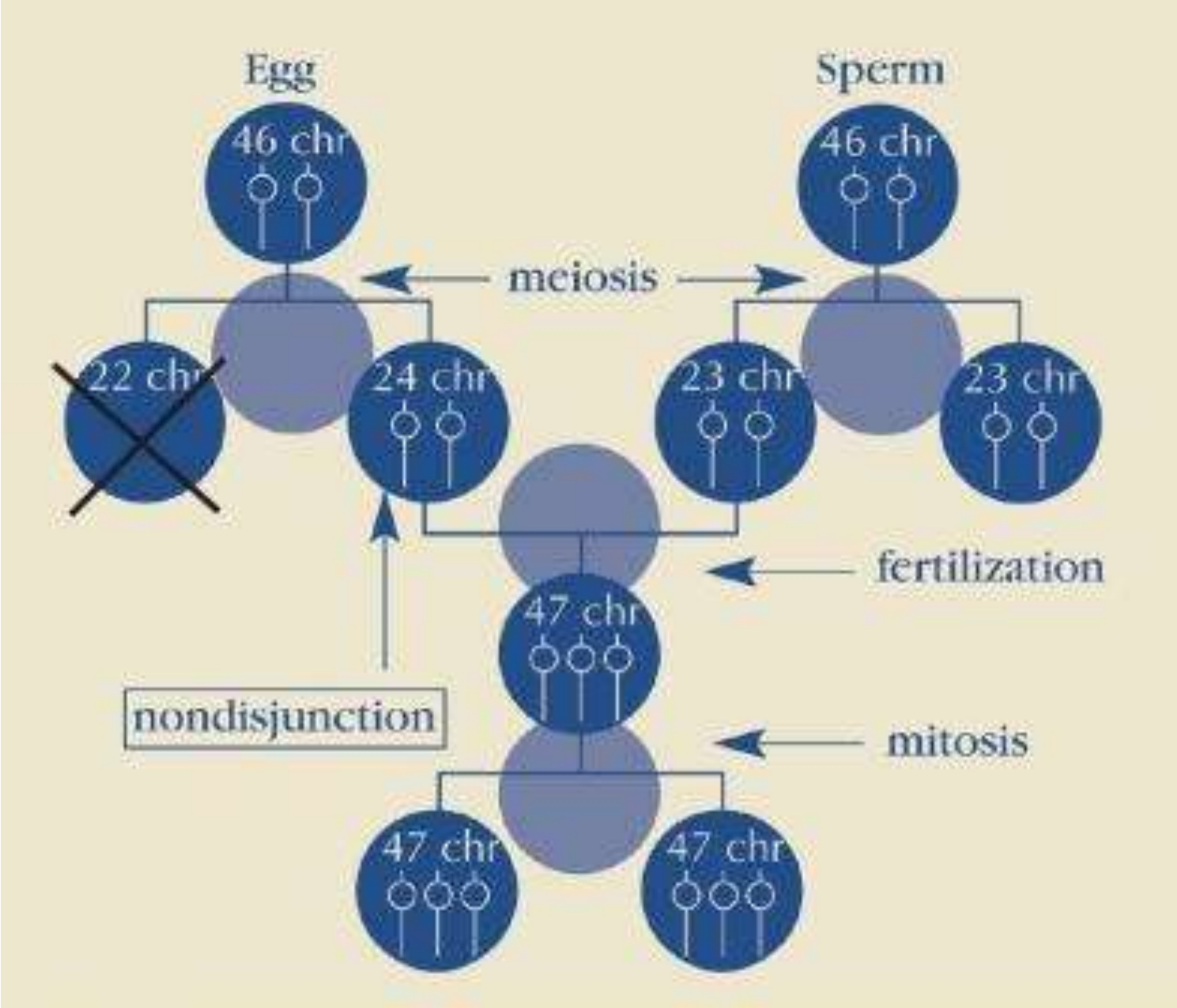


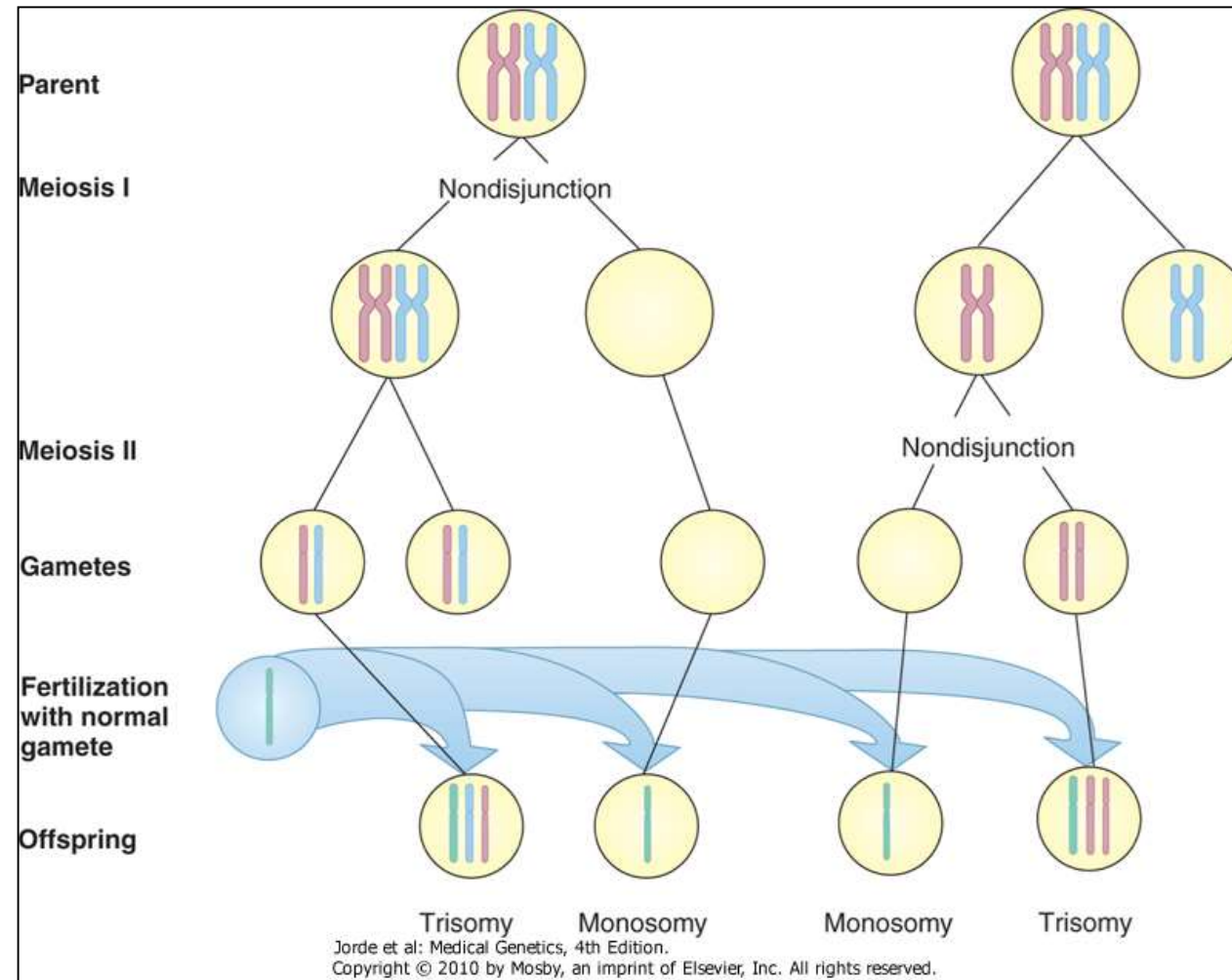
1 in 770 babies



Maternal Age and Nondisjunction







Trisomy

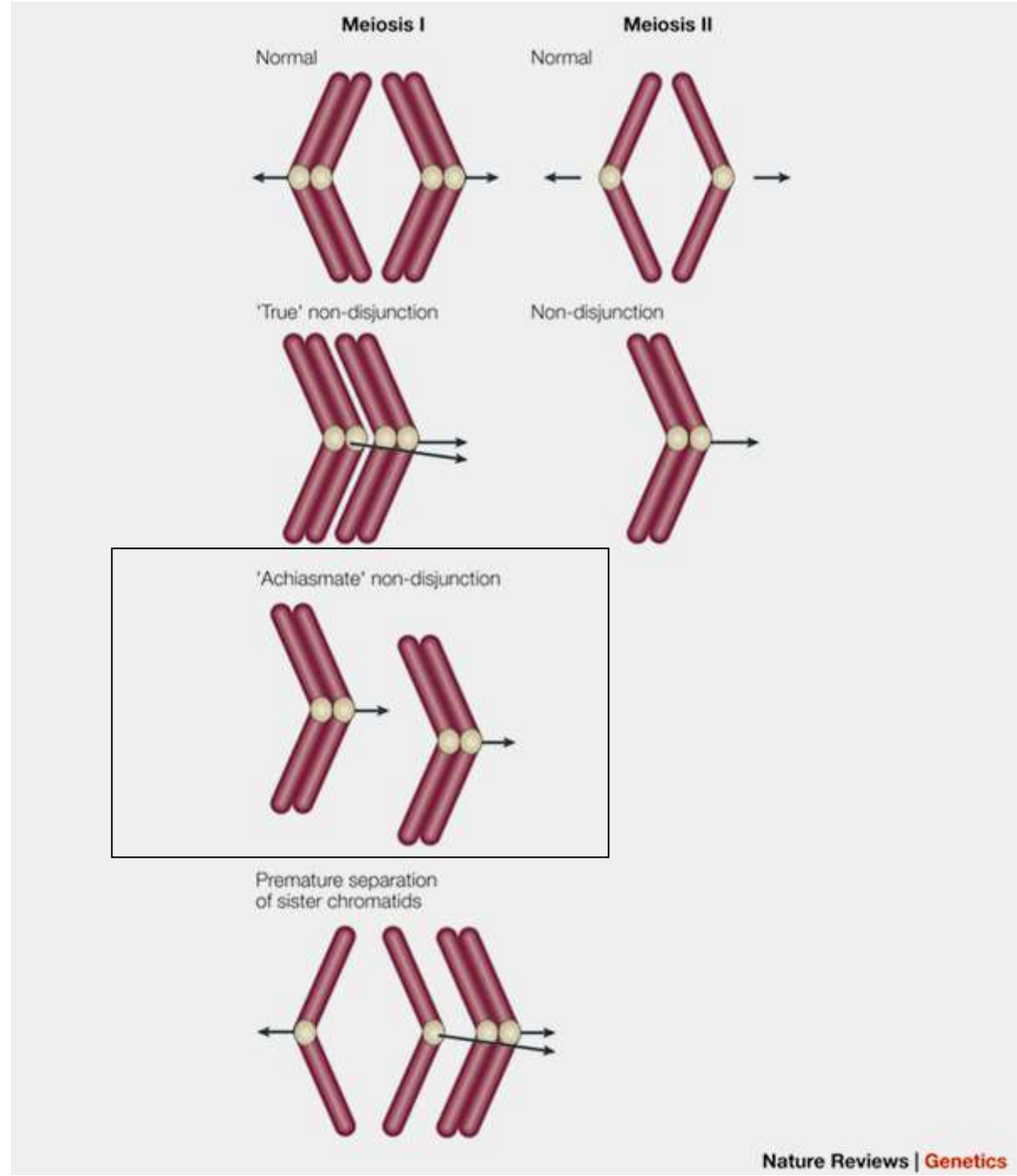
Maternal Errors: 94% of cases

- MI 64% *→ more frequent during MI*
- MII 19%
- Indeterminate 11%

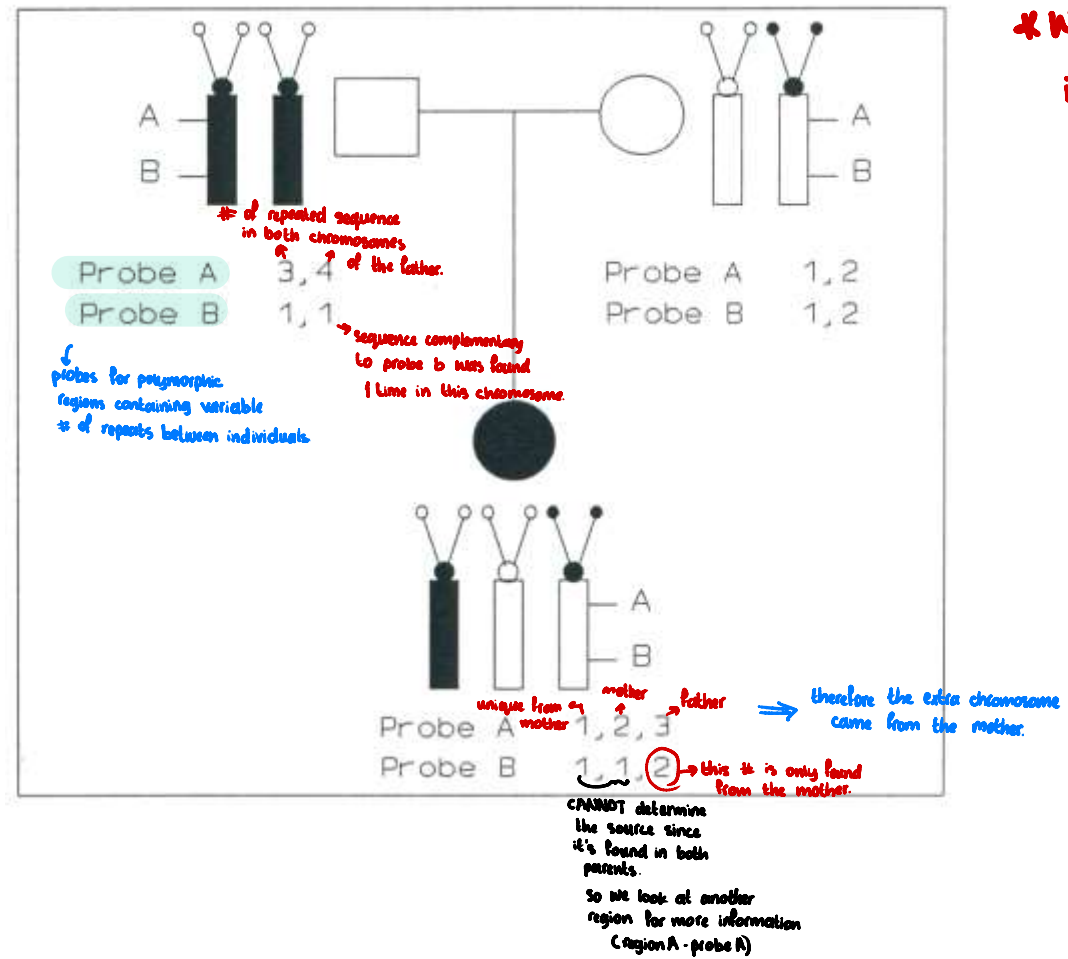
Paternal Errors: 4.5% of cases

- MI 1%
- MII 3.5%

Unknown: 1.5%



Causal Factors in Nondisjunction



* we can tell whether non-disjunction is from a paternal or maternal source by studying these 3 chromosomes & comparing them to parents.

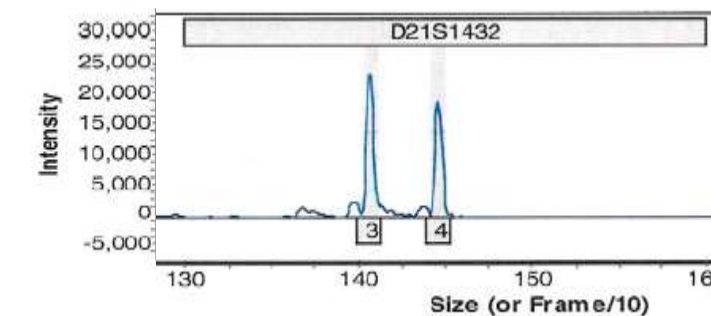
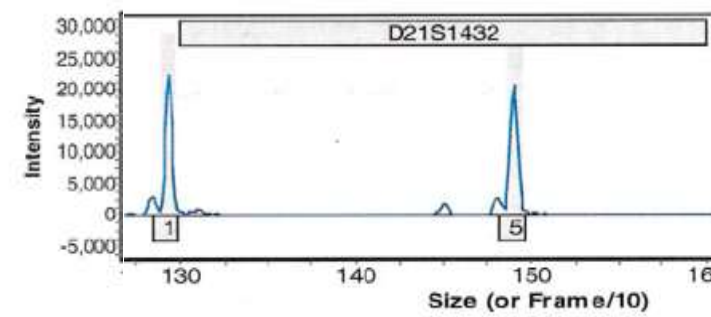
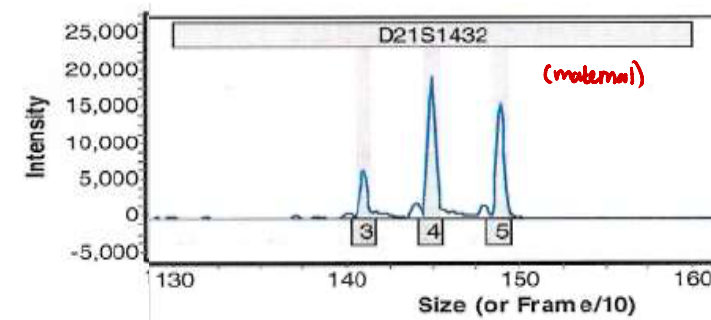
Evaluate the Origin of the Extra Chromosome Using Polymorphic Markers

Proband

proband in genetics:
individual who brings family
to clinical attention.
(Typically but not always the patient)

Father

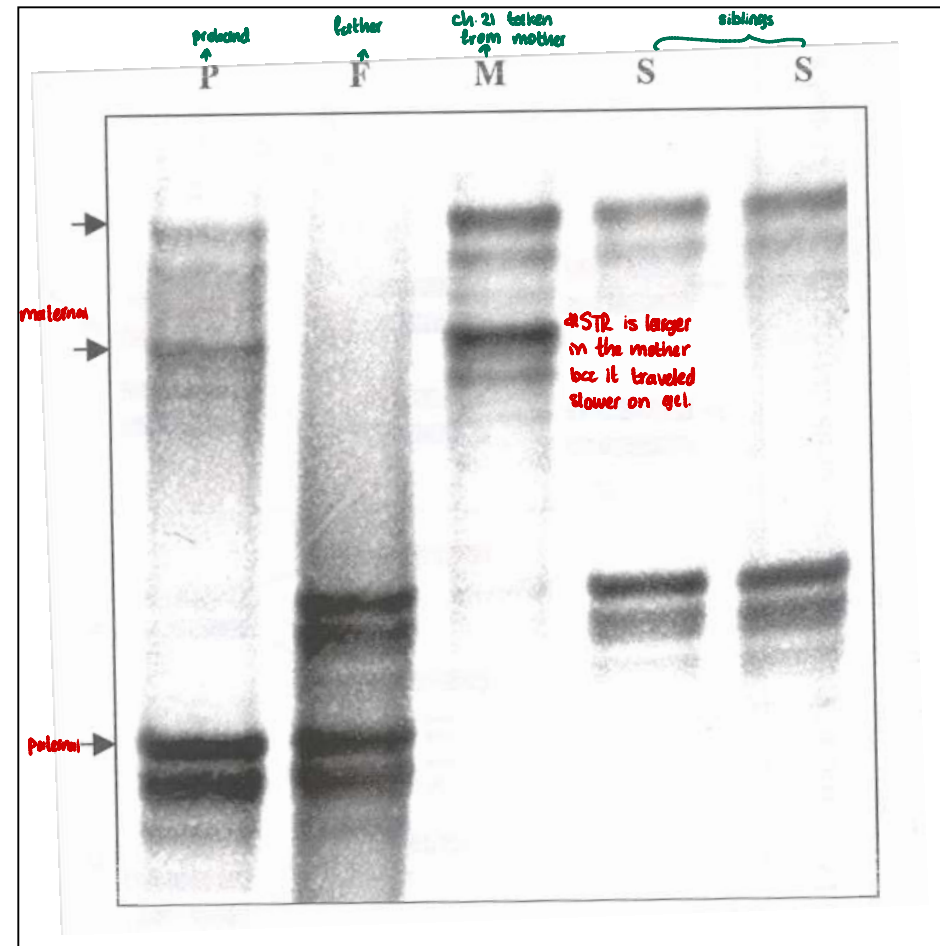
Mother



D21S1432 Tetranucleotide ^{Short tandem repeat probe} STRP

DNA markers can be used to determine the parental origin of the extra chromosome in trisomic individuals

→ gel electrophoresis



→ we design a primers which point out repeated regions
the size of these repeated regions is variable in individuals
↓
location of bands is different due to variation in size.

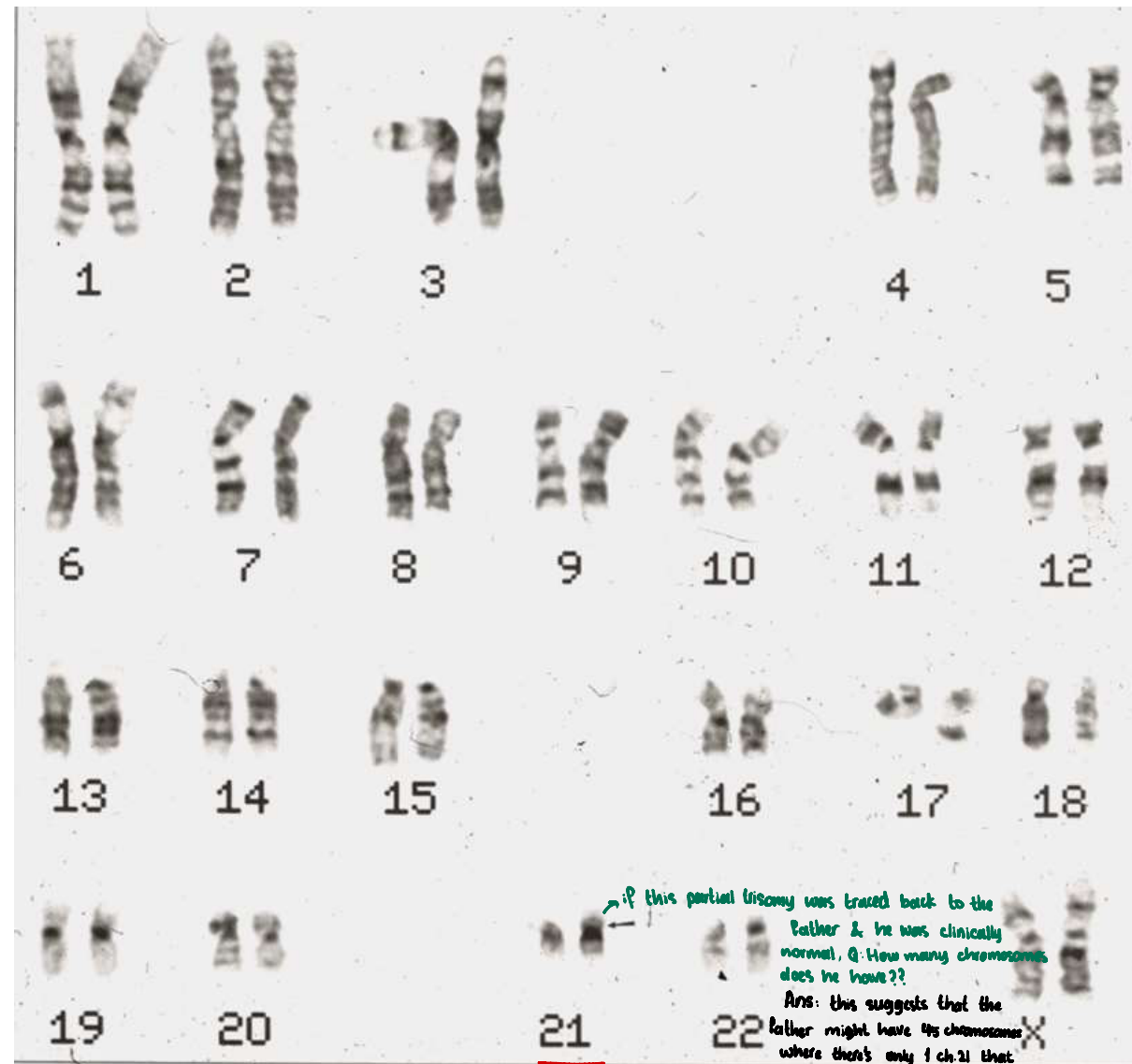
Trisomy	n	Maternal		Paternal		PZM (%)
		MI (%)	MII (%)	MI (%)	MII (%)	
<i>Acrocentrics</i>						
13	74	56.6	33.9	2.7	5.4	1.4
14	26	36.5	36.5	0.0	19.2	7.7
15	34	76.3	9.0	0.0	14.7	0.0
21	782	69.6	23.6	1.7	2.3	2.7
22	130	86.4	10.0	1.8	0.0	1.8
<i>Non-acrocentrics</i>						
2	18	53.4	13.3	27.8	0.0	5.6
7	14	17.2	25.7	0.0	0.0	57.1
8	12	50.0	50.0	0.0	0.0	50.0
16	104	100	0.0	0.0	0.0	0.0
18	150	33.3	58.7	0.0	0.0	8.0

*Adapted from Hall *et al.* (6). MI, meiosis I; MII, meiosis II; PZM, post-zygotic mitotic.



Partial Trisomy 21 (21q)

* trisomy 21 non-disjunction due to advanced maternal age is NOT applicable to other chromosomal non-disjunction.



2 entities are seen (no extra chromosome) in this scenario the centromere is attached to 2 q arms → this is due to an abnormal chromosomal arrangement in 1 of the parents (probably)

3 q arms which is equivalent to 3 ch.21 bcz q arms are more significant than p arms in a clinical pov.

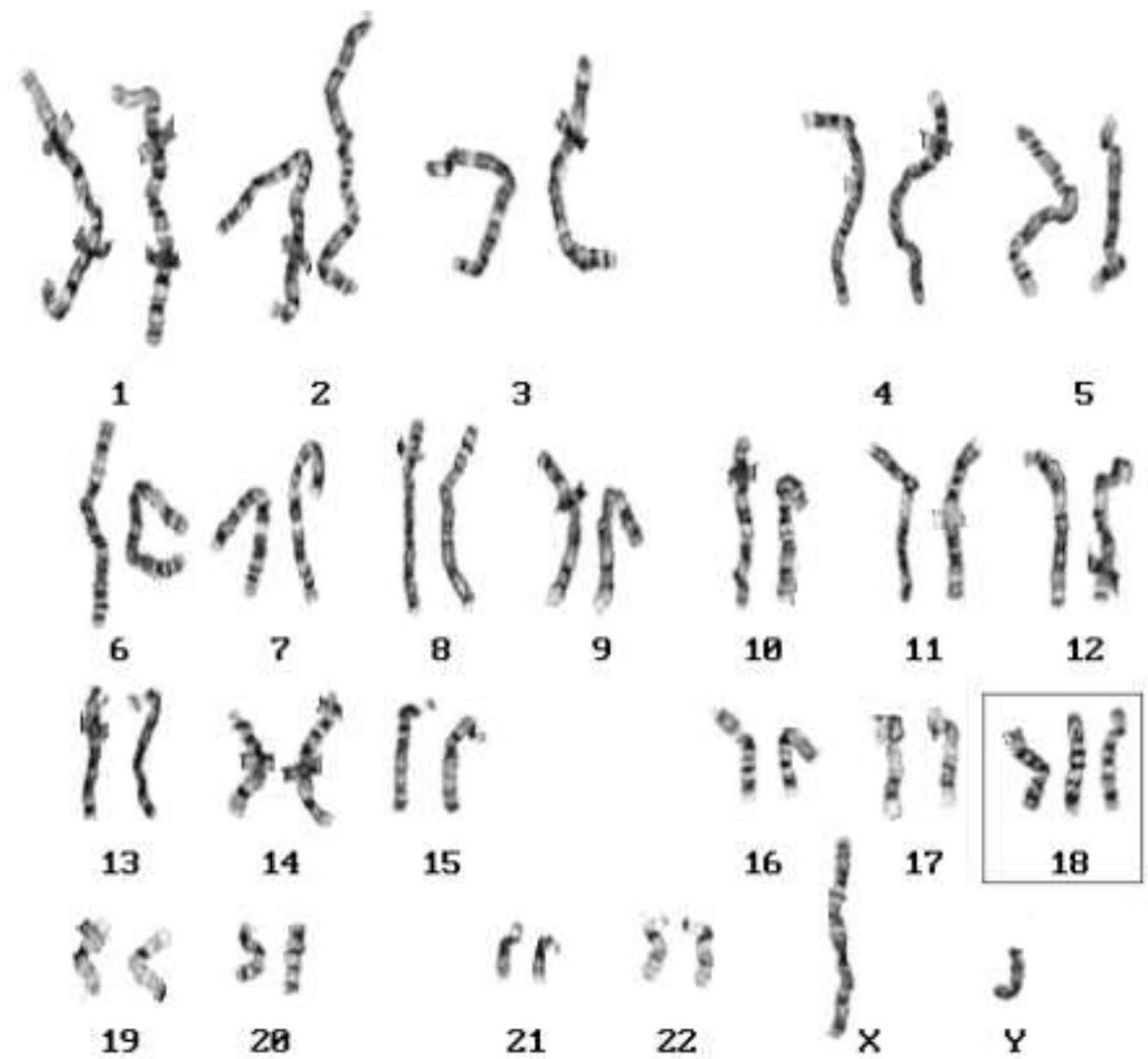
reminder: ch.21 is acrocentric

* in partial trisomy → pt has 46 chromosomes BUT ch.21 contains 3 q arms which is equivalent to an entire 3rd extra chromosome.

if this partial trisomy was traced back to the father & he was clinically normal, Q: How many chromosomes does he have??

Ans: this suggests that the father might have 45 chromosomes where there's only 1 ch.21 that has 2 q arms on its own which manifests as clinically normal

spermatogenesis → 50% of sperms will carry double q arm.
→ 50% of sperms will be w/o ch.21



Karyotype: 47,XY,+18
extra ch. 18

Trisomy 18 (Edward syndrome)

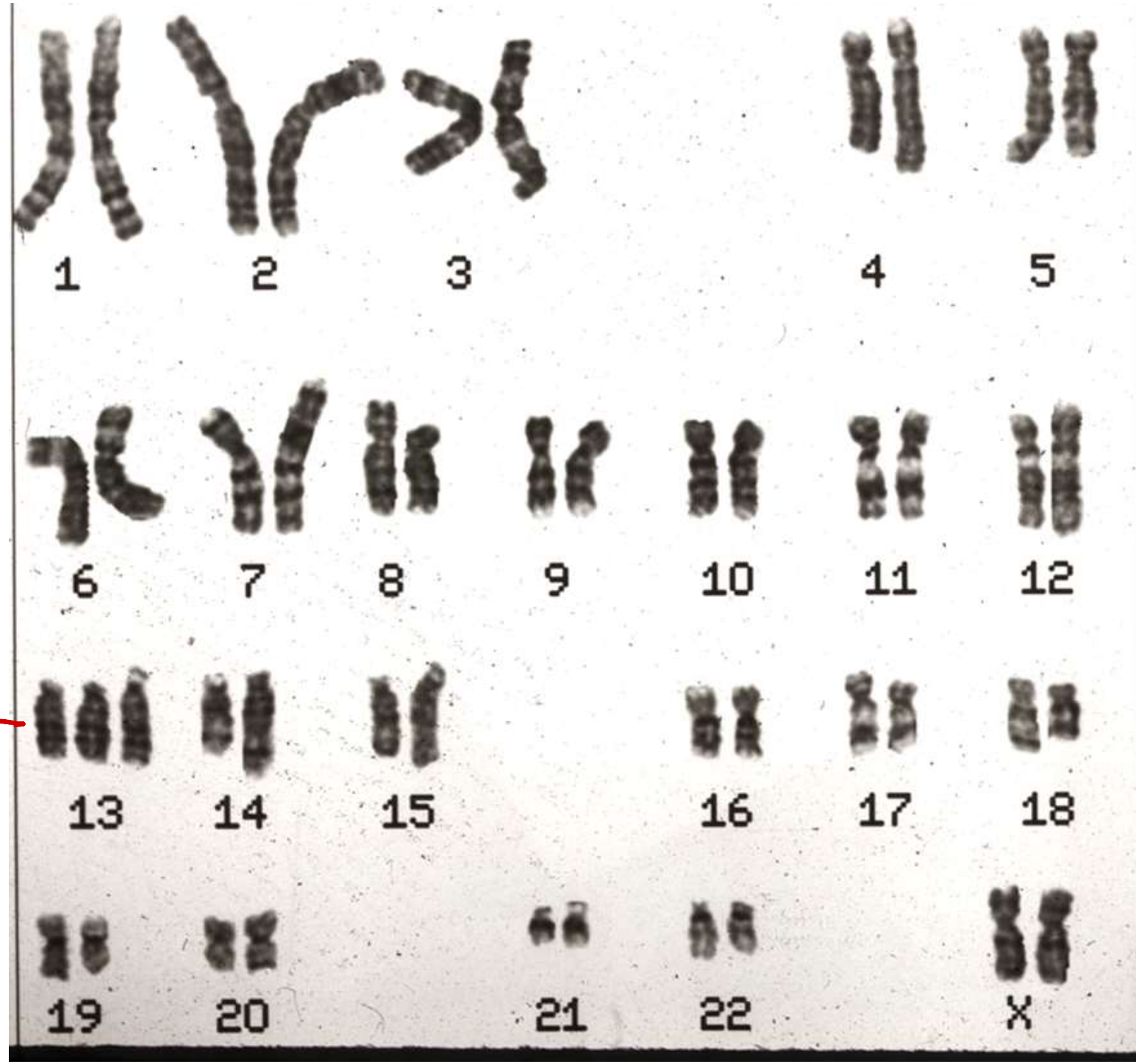


Findings:

CHD (95%)
Failure to thrive (FTT) ↓ weight & size
Mental retardation
Growth retardation
Hypertonia ↑ muscle tone, rigidity
Prominent Occiput



Low-set, malformed ears
Short sternum
Intestinal Abnormalities
Unusual hand position → "clenched fist"
Rocker bottom feet



trisomy 13 ←

Trisomy 13, 18, & 21 are the ONLY viable autosomal numerical abnormalities.



↳ this does NOT mean that non-disjunction is only seen in them.

↳ Trisomy could happen to any chromosome but only these 3 chromosomes make it to life.

Trisomy 13 (Patau syndrome)

↳ monosomy could also happen to these chromosomes but those are lethal & don't make it to birth.

(more deleterious than trisomy)

↳ a missing genetic material is worse than an extra genetic material.



Findings:

- CHD (85%)
- Mental retardation
- Hyper- or hypotonia
- Scalp defects
- Microcephaly
- Small eyes
- Low-set, malformed ears
- Cleft lip/palate
- Polydactyly and syndactyly
- Polycystic kidneys
- Rocker-bottom feet

↳ commonly seen in chromosomal abnormalities

