TERATOGENESIS

ONTOGENESIS

Inborn developmental defects

- Occured during prenatal development
- Are present by delivery
- At about 3-5 % newborns are affected.

Inborn developmental defects

1. CHROMOSOMAL ABERRATIONS (0,6 %)
   - changes in number – aneuploidy, changes in structure

1. MONOGENIC DISORDERS (0,6-0,8 %)
   - familiar incidence, risk of recurrence, new mutations, autosomal or X-linked inheritance

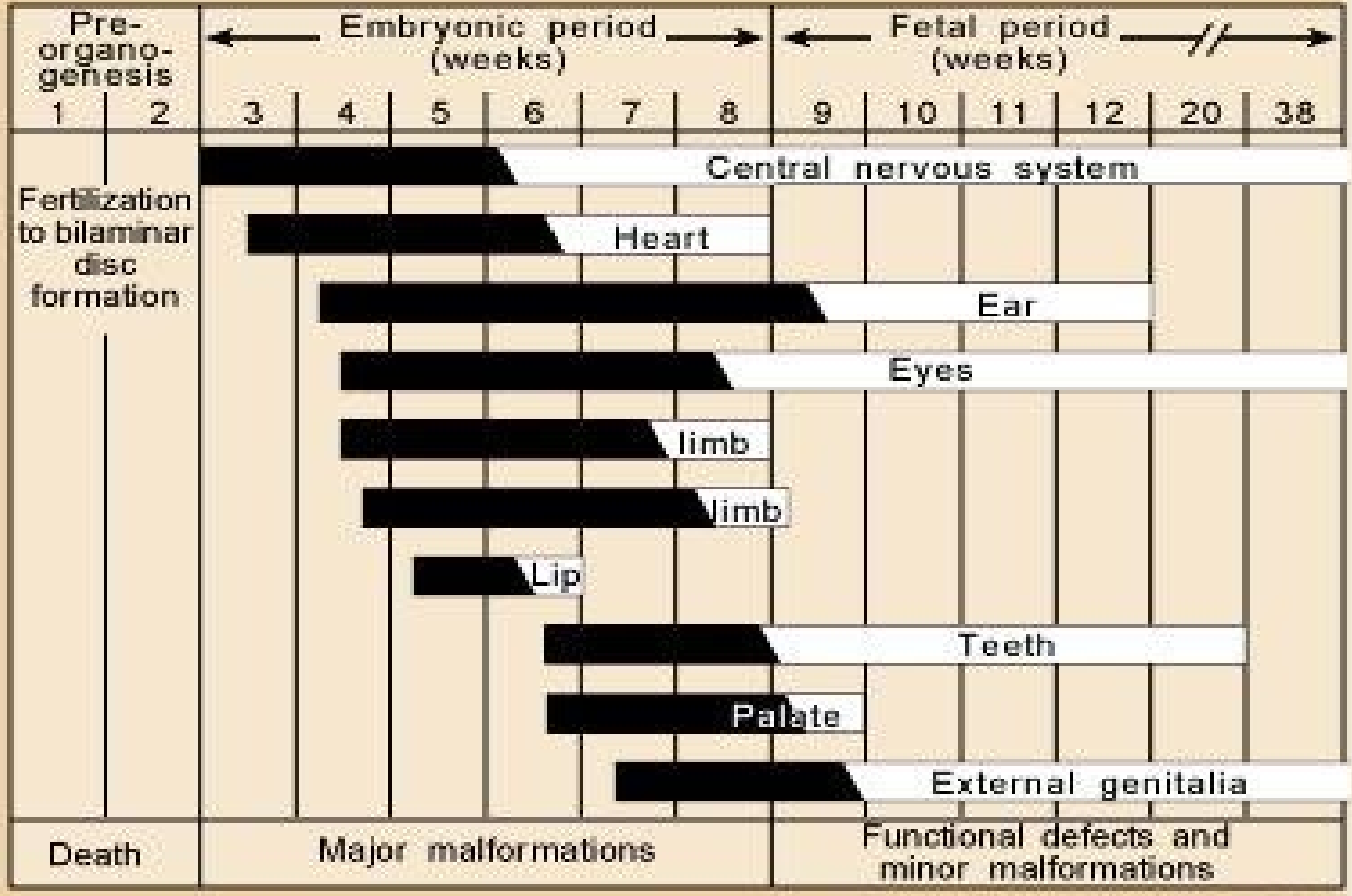
1. MULTIFACTORIAL TRAITS (2-4 %)
   - interaction of genetic and external factors, cleft lip/palate

1. EXOGENIC FACTORS (0,2 %)
   - teratogenes

Causation of defects

- **Mutations – genetic code is changed**
- **Teratogenes – factors of external environment - genetic code is not changed**

SUSCEPTIBILITY TO TERATOGENESIS FOR ORGAN SYSTEMS
(Solid bar denotes highly sensitive periods)



Sadler 1990

Teratogenes

Physical

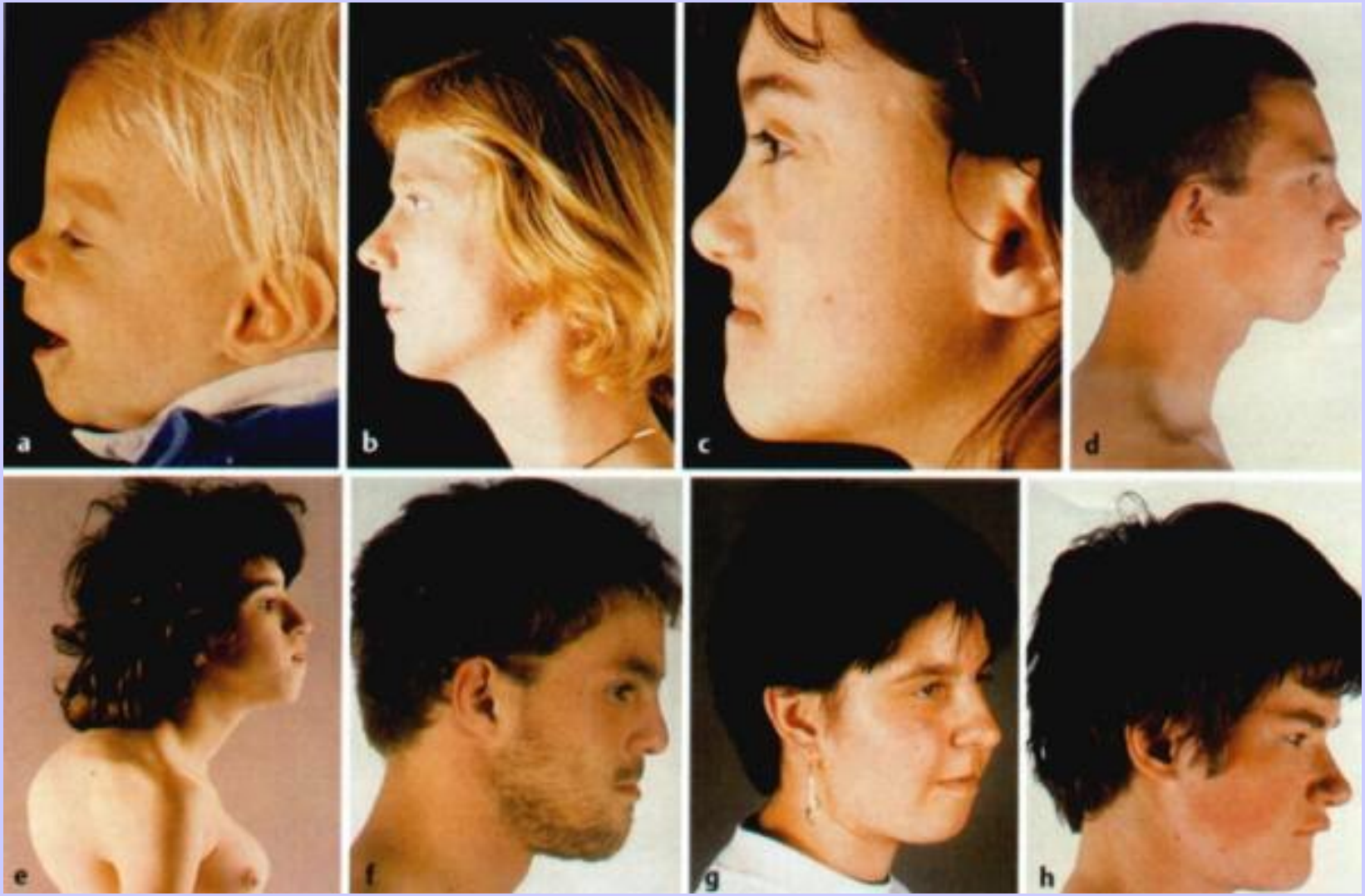
- radiation
  - Ionizing radiation
  - X-rays
- high temperature - (39° C)

Teratogenes

Chemical:

- **drugs (e.g. antibiotics, antiepileptics, cytostatics, warfarine, ACE inhibitors, vit. A, retinoids);**
- **alcohol and (street drugs).**
- **practically all chemical matters**

Fetal alcohol syndrome (FAS)



Fetal alcohol syndrome (FAS)

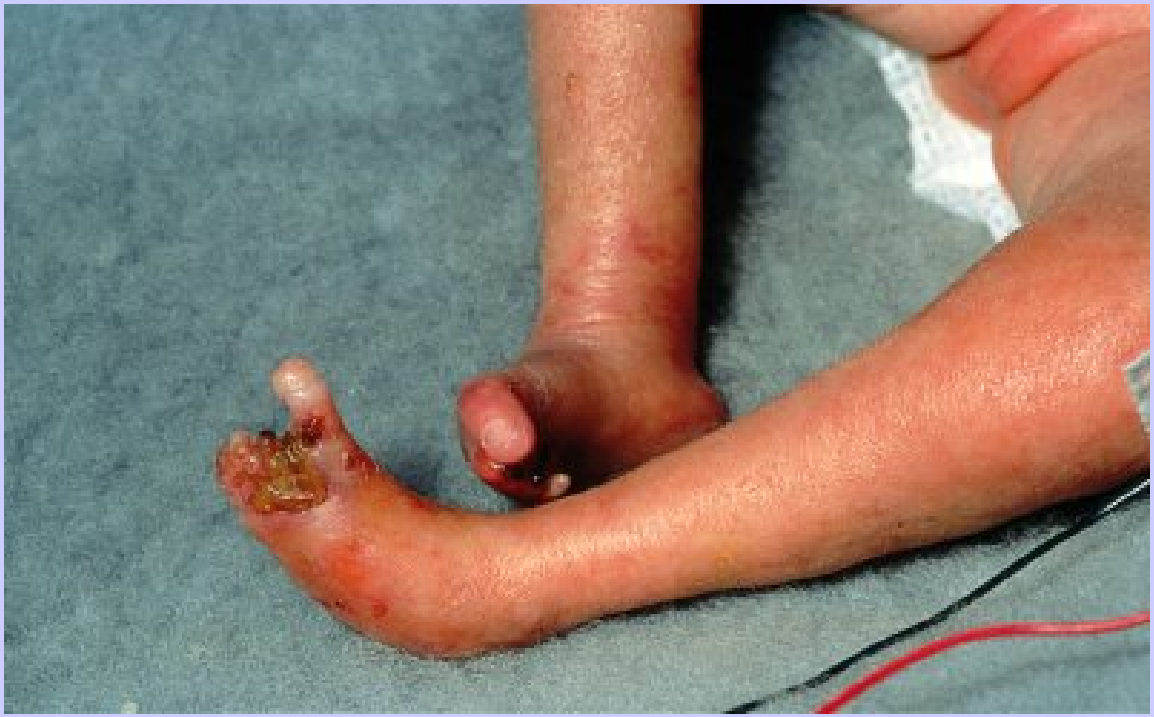
Teratogenes

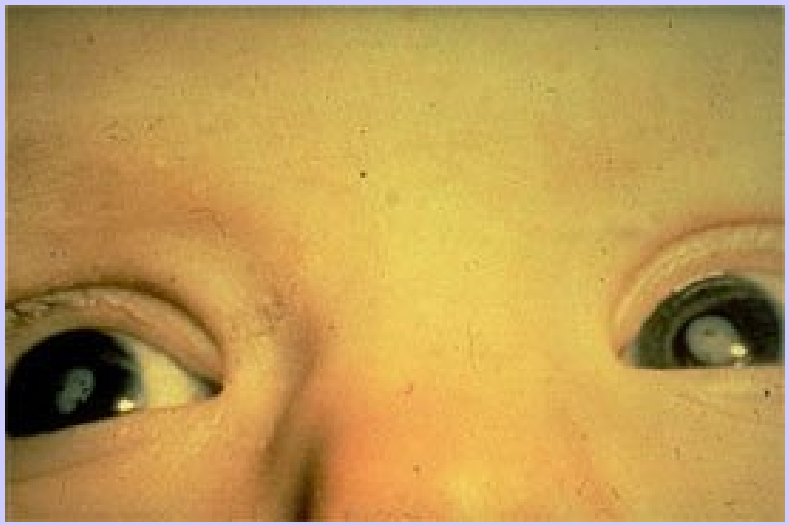
Biological

- **maternal infections**
  - **toxoplasmosis (*Toxoplasma gondii*),**
  - **rubella (German measles, *Rubivirus*),**
  - **syphilis(*Treponema pallidum*),**
  - **AIDS (*HIV*)**
  - **infections caused by herpes viruses**
  - **infections caused by EB viruses, CMV**
- **maternal diseases – e.g. diabetes mellitus, phenylketonuria**

Maternal infection – rubella (congenital rubella syndrome)

deafness, blindness,
heart defects,
mental retardation,
growth deficits





Examples of human inherited developmental disorders

Teratogenic effect of thalidomide

Teratogenic effect of thalidomide

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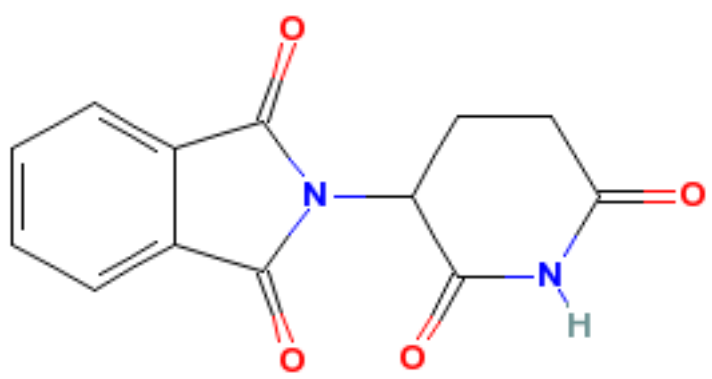
sedative drug thalidomide administered during pregnancy



- limb abnormalities (amelia)
- oesophagus atresia
- kidney agenesis
- etc.

One drug, wide variety of malformations - why?

-"critical periods" of organ development

Why were only 10-50 % babies in risk malformed?

- genetic factors conferring different susceptibility

Why was the teratogenic effect not revealed during preclinical testing on rodents?

- species-dependent susceptibility – use more species for testing!

Incontinentia pigmenti (sy. Bloch-Schulzberger)

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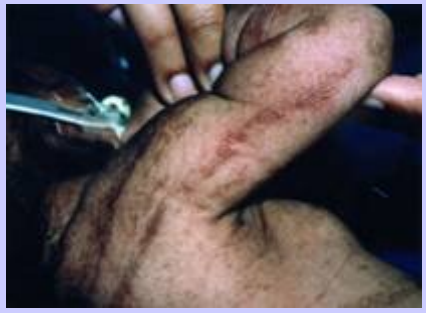
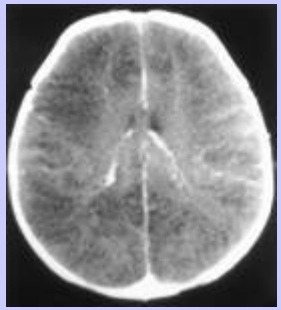
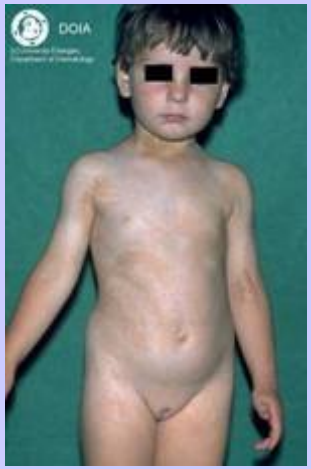




- only women afflicted
- vesiculous exanthema in babies
- cerebral infarctions leading to mental retardation



- marble-cake like skin (older age)
- many other symptoms
- offspring of affected females – distorted sex ratio boys:girls 1:2, many early abortions

What´s the type of inheritance?

X-linked dominant

lethal in males

	X^+	Y
X^+	X^+X^+	X^+Y
X^{IP}	$X^{IP}X^+$	~~$X^{IP}Y$~~

Complete androgen insensitivity syndrome

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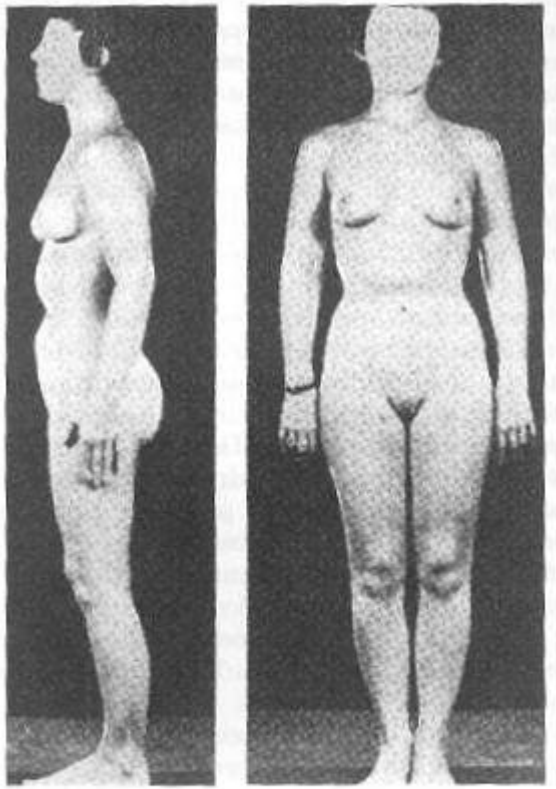
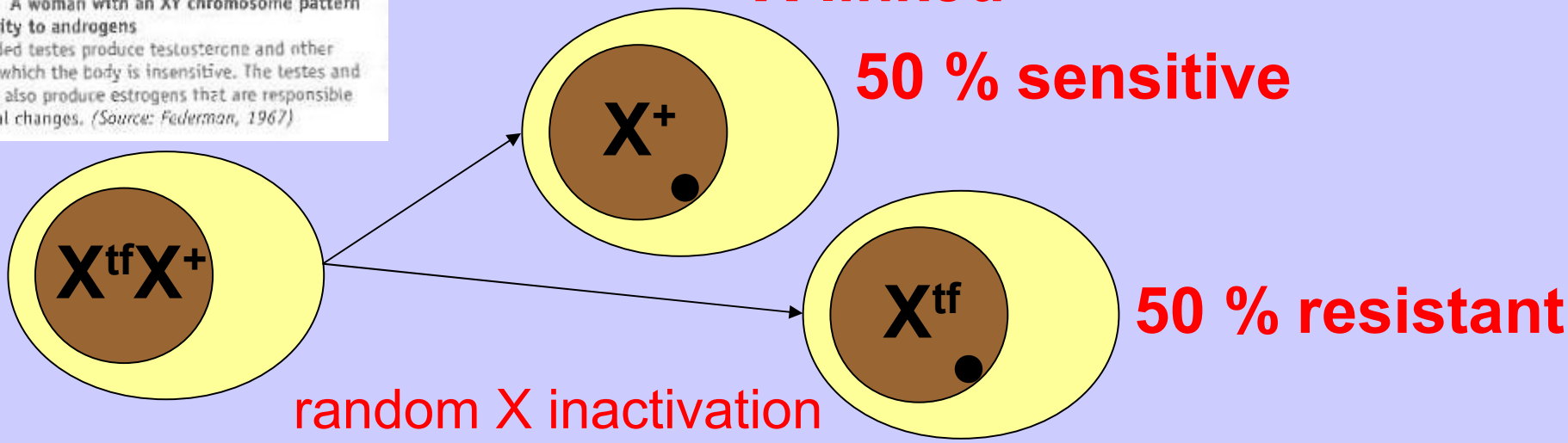


Figure 11.10 A woman with an XY chromosome pattern but insensitivity to androgens
Two undescended testes produce testosterone and other androgens, to which the body is insensitive. The testes and adrenal glands also produce estrogens that are responsible for the pubertal changes. *(Source: Federman, 1967)*

- female phenotype, but:
- primary amenorrhea
- uterus and oviducts absent
- no pubic and axillary hair
- karyotype 46, XY
- undescended testes
- cells insensitive to testosterone

Only 50 % cells of the mother sensitive to testosterone - WHY?

X-linked



Complete androgen insensitivity syndrome

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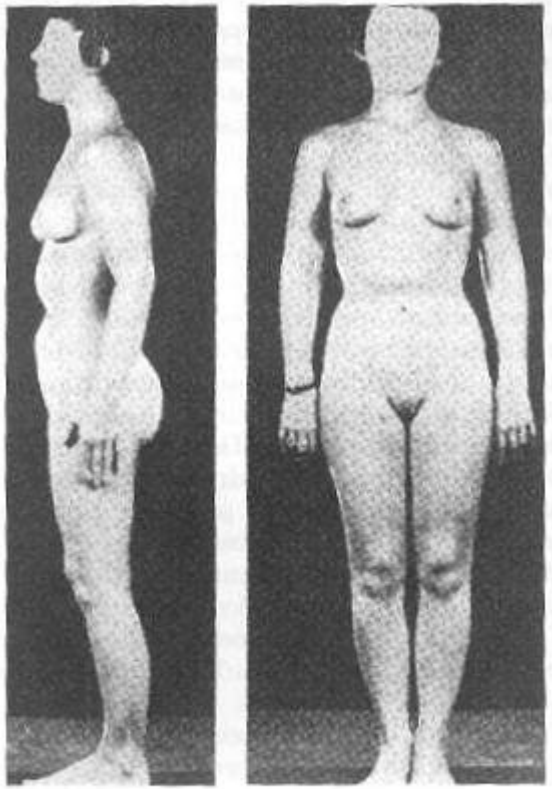

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  - primary amenorrhea
  - uterus and oviducts absent
  - no pubic and axillary hair
  - karyotype 46, XY
  - undescended testes
  - cells insensitive to testosterone
  - only 50 % cells of the mother sensitive to testosterone

What´s the mode of inheritance?

X-linked recessive

	X^+	Y
X^+	X^+X^+	X^+Y
X^{tf}	$X^{tf}X^+$	$X^{tf}Y$

Complete androgen insensitivity syndrome

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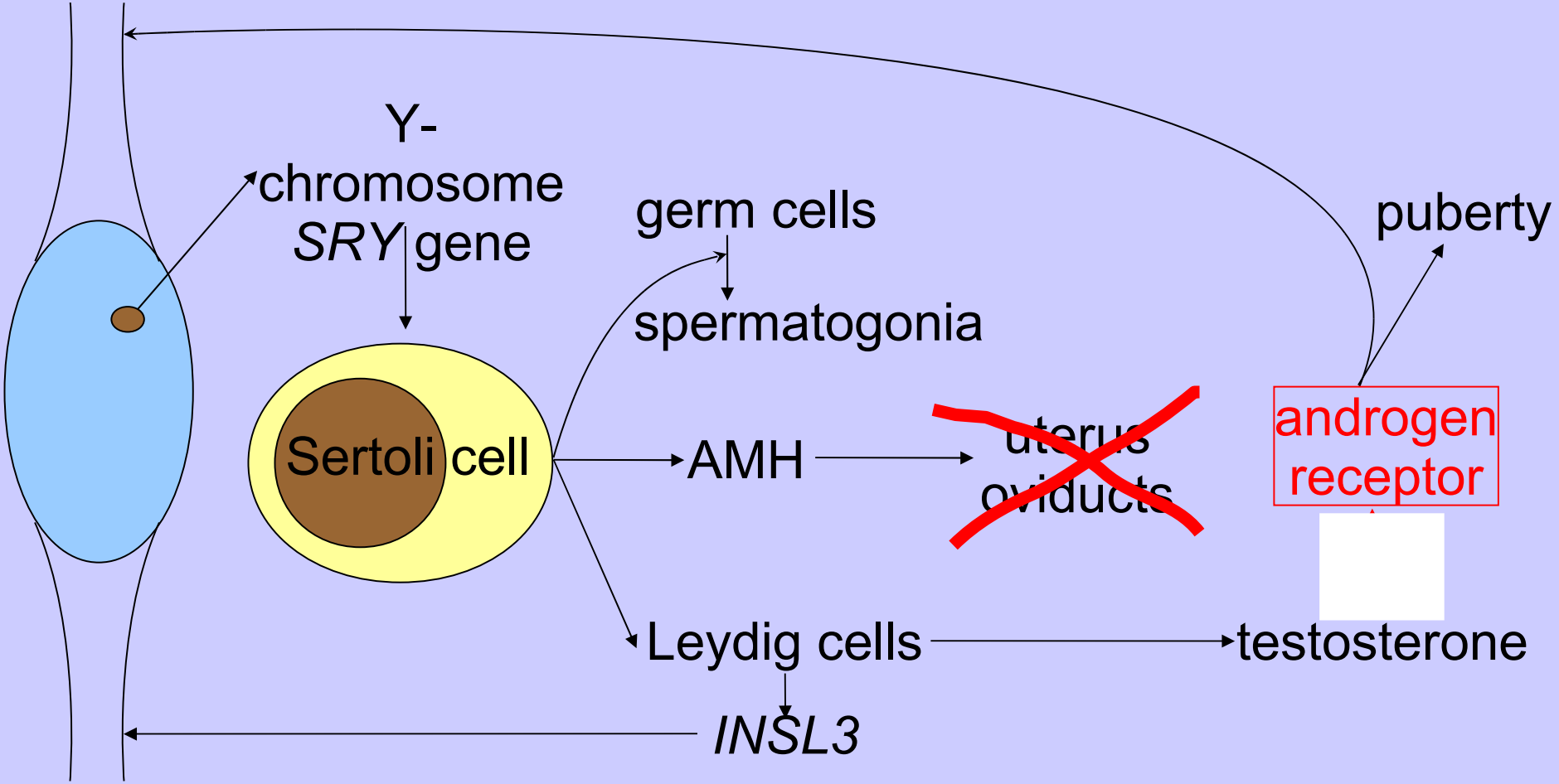
Why testes develop despite androgen resistance?



gonad differentiation depends on SRY gene on Y chromosome.
Testosterone is responsible for descent, development of external genitals and pubertal changes

Anhidrotic ectodermal dysplasia

task 4, page 166

In males:

- missing sweat glands
- hypertermia
- serious course of (otherwise banal) infections
- abnormal dentition

In females:

- missing sweat glands, in patches
- the pattern of skin without sweat glands differs between monozygotic twins

What´s the mode of inheritance?

X-linked

	X^+	Y
X^+	X^+X^+	X^+Y
X^{eda}	$X^{eda}X^+$	$X^{eda}Y$

Anhidrotic ectodermal dysplasia

task 4, page 166

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In females:

- missing sweat glands, in patches
- the pattern of skin without sweat glands differs between monozygotic twins

Why is there different pattern in female monozygotic twins?

- Random X inactivation

Are there any differences between male monozygotic twins?

- no, they´ve no sweat glands at all

(hemizygotes for X chromosome with mutant gene)