Developmental genetics

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Institute of Biology and Medical Genetics

Lesson from an experimental animal model

Task 1, page 159, Phenotypes of polydactylous rats

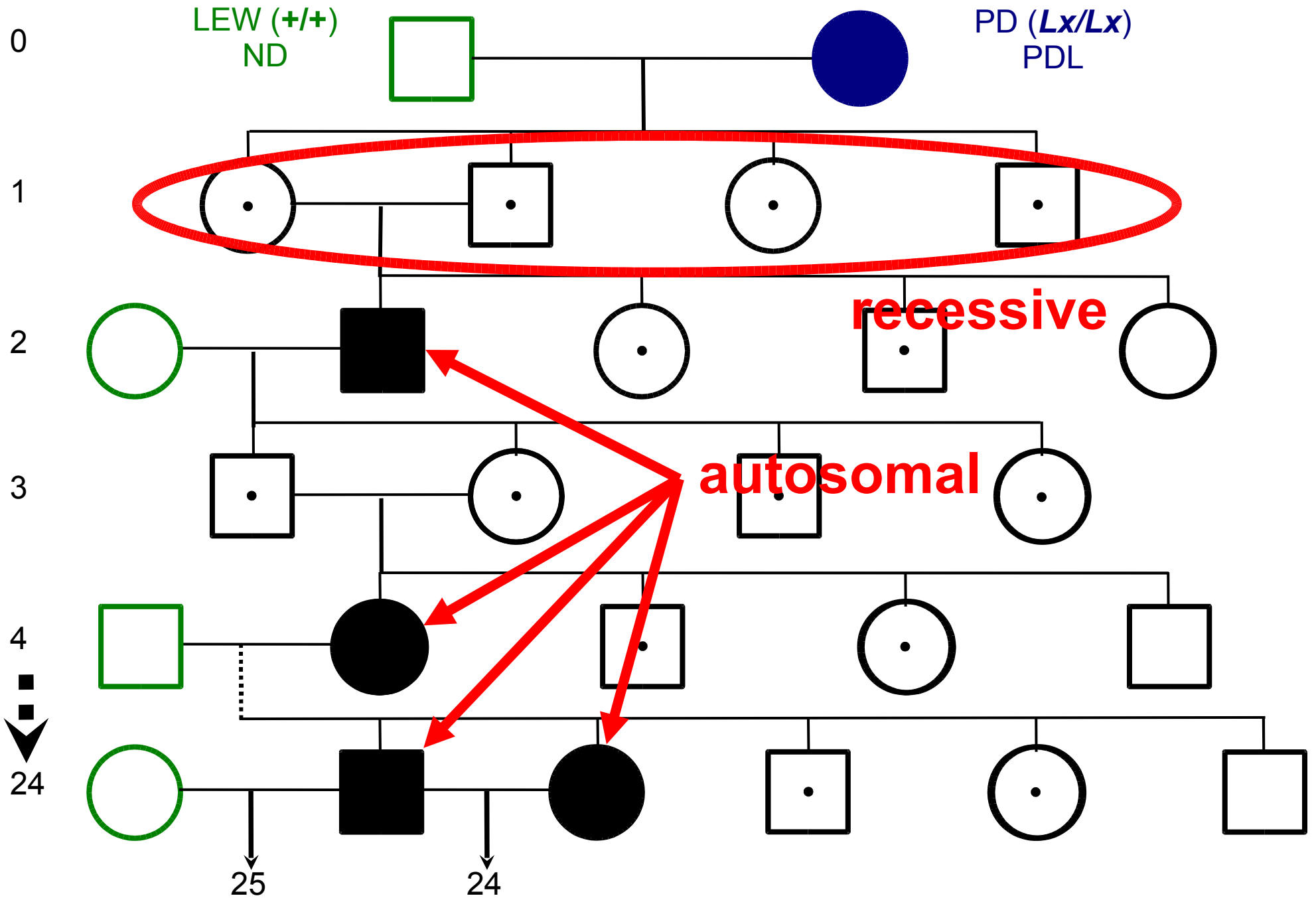
LEW

PD

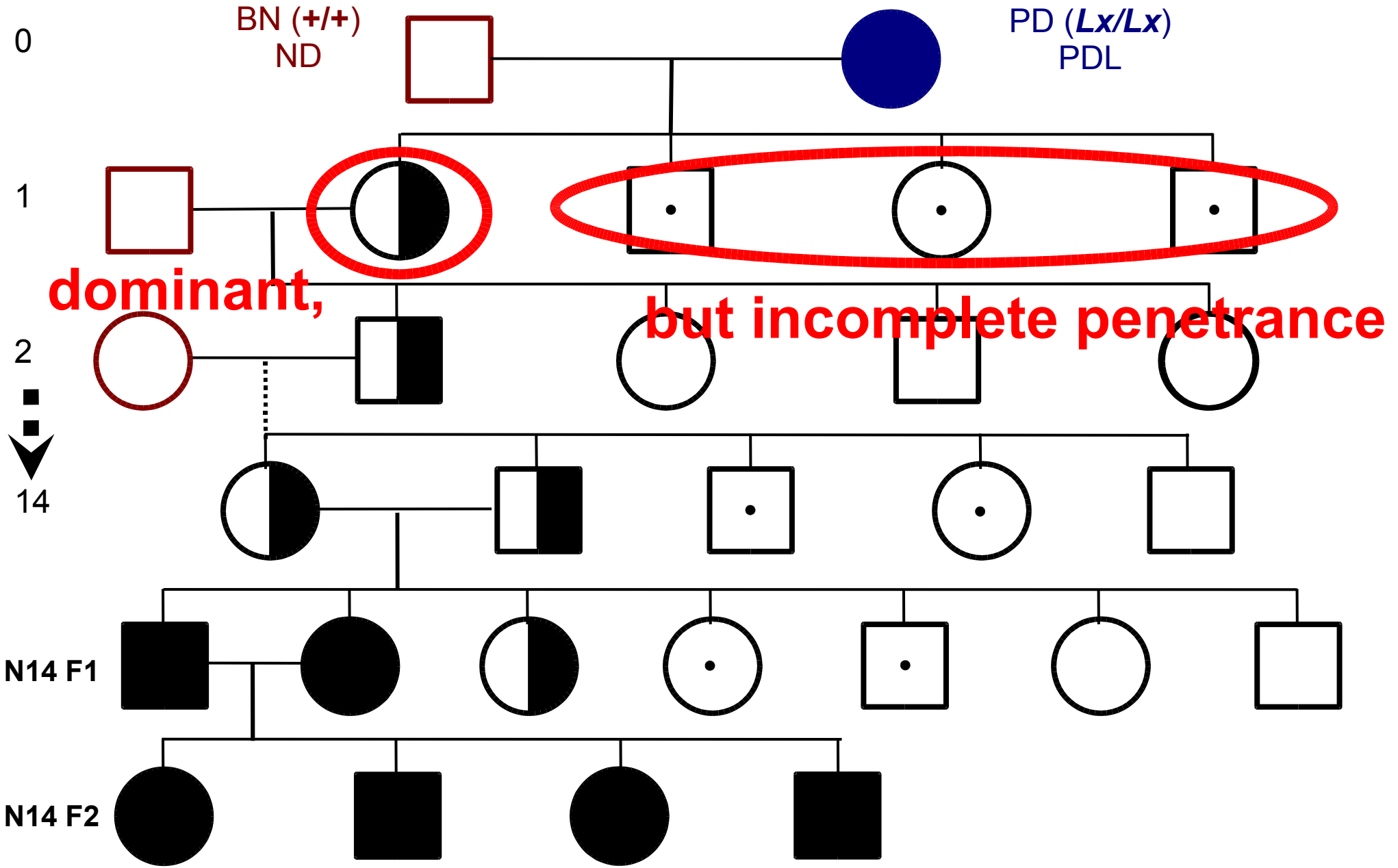
LEW.*Lx*

BN.*Lx*

Production of LEW.*Lx* congenic strain



Production of BN.*Lx* congenic strain



Phenotypes of polydactylous rats, continued

strain	number of digits				"luxation" of hin
	front		hind feet		
LEW, BN	4	4	5	5	0%
PD	4	4	5T	5T-6	100%
LEW.*Lx* (*Lx/Lx*)	4	4	6-7	7	10%
LEW.*Lx* (*+/Lx*)	4	4	5	5	0%
BN.*Lx* (*Lx/Lx*)	5	5	6	6	100%
BN.*Lx* (*+/Lx*)	4	4	6-7	6	0%

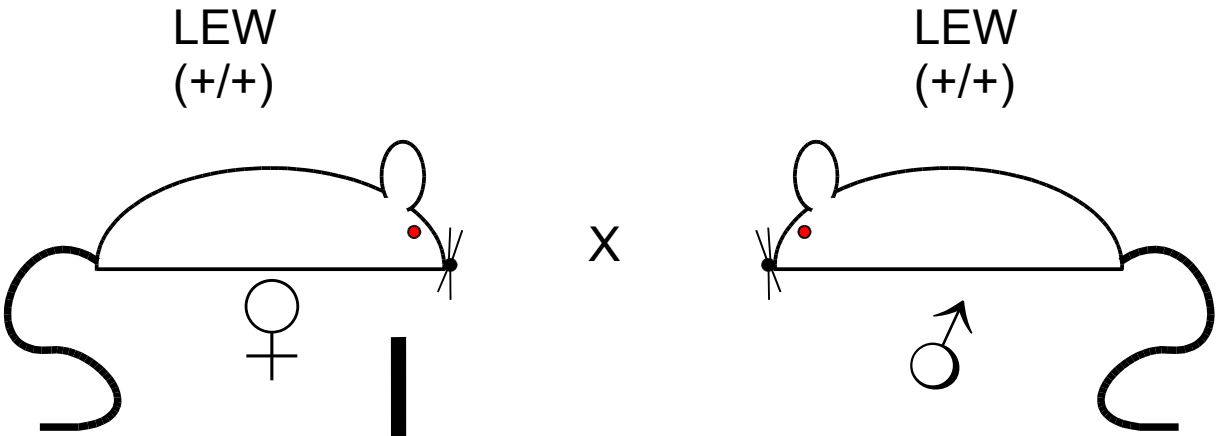
5T = 5 digits, but triphalangeal thumb

F_1 hybrids

ND = normal digits ("normodactyly")
PD = polydactyly

Teratogenic effect of a mutagenic drug

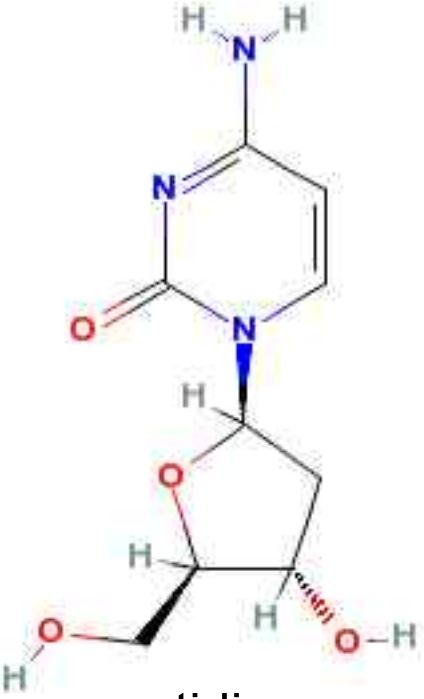
task 2, page 164



12th embryonic day
5-BrdU

80%
normal

20%
polydactyly



cytidine

Teratogenic effect of a mutagenic drug

task 2, page 164

How do we call this result of drug action?

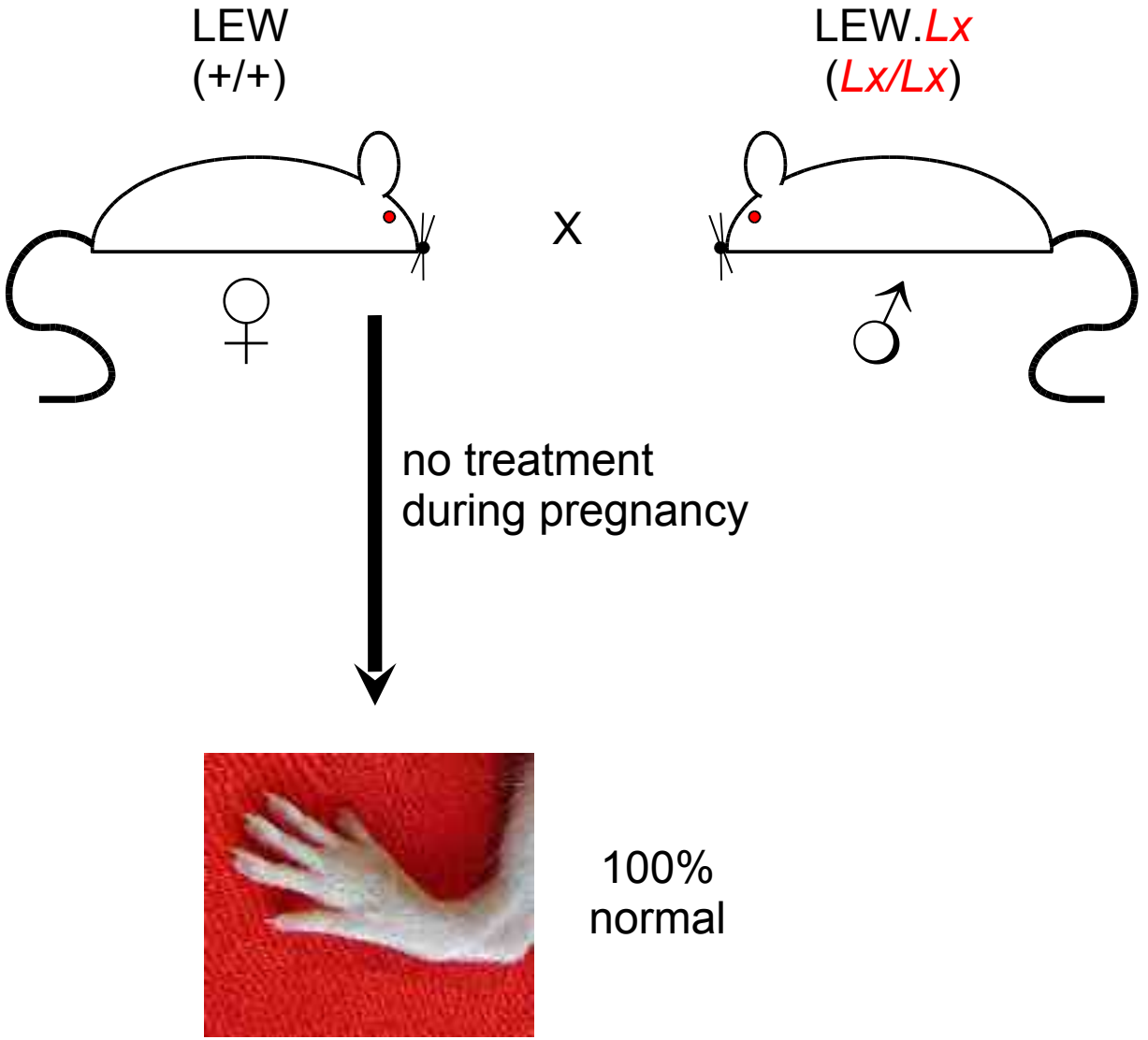
PHENOCOPY

What phenotype do you expect in offspring of the drug-induced polydactylous rats?

NORMAL

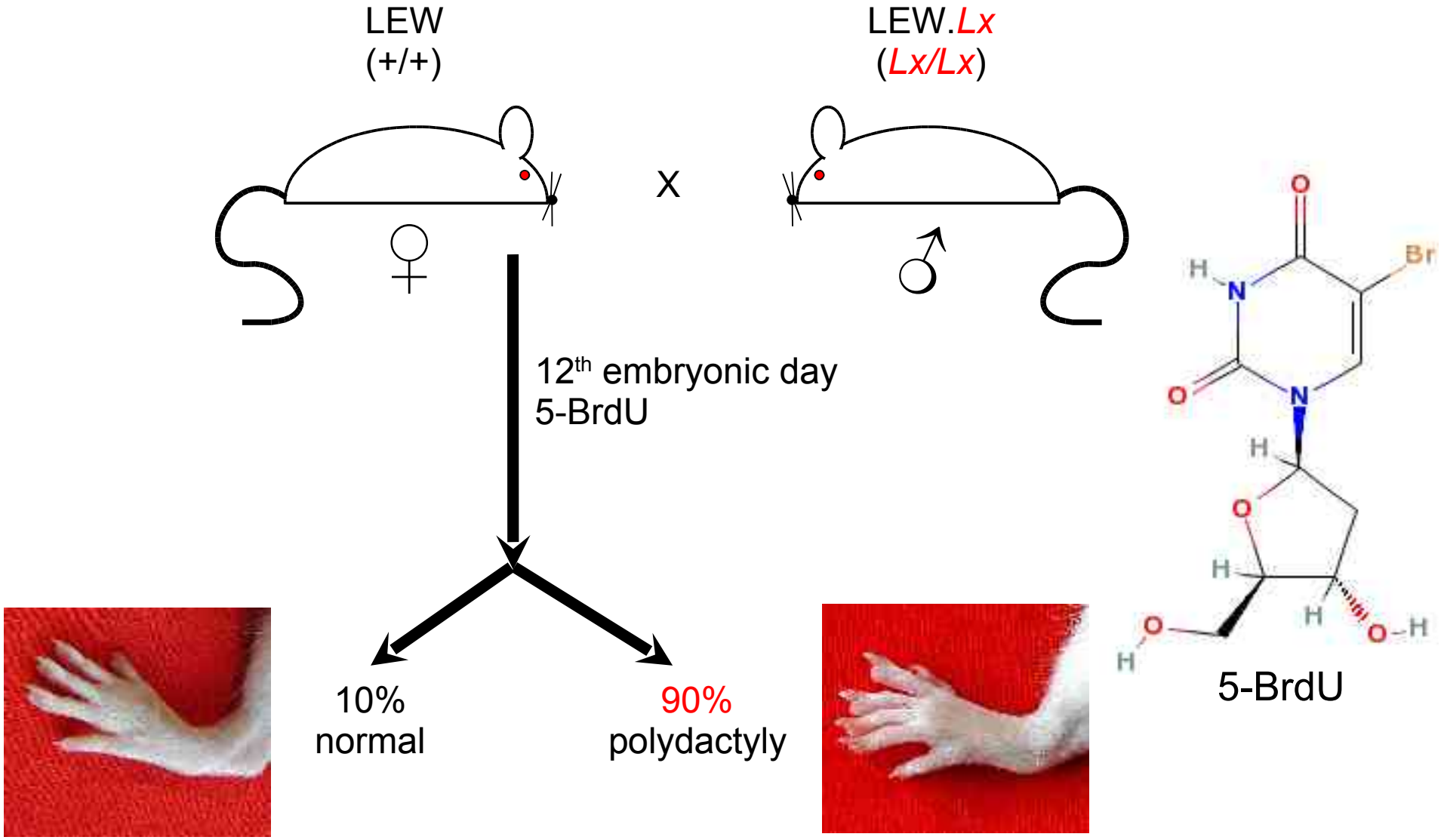
Interaction of a mutant allele with a teratogen

task 3, page 164



Interaction of a mutant allele with a teratogen

task 3, page 164



Interaction of a mutant allele with a teratogen

task 3, page 164

ND x ND	ND x PD	PD x PD

What limb phenotype do we expect in offspring?

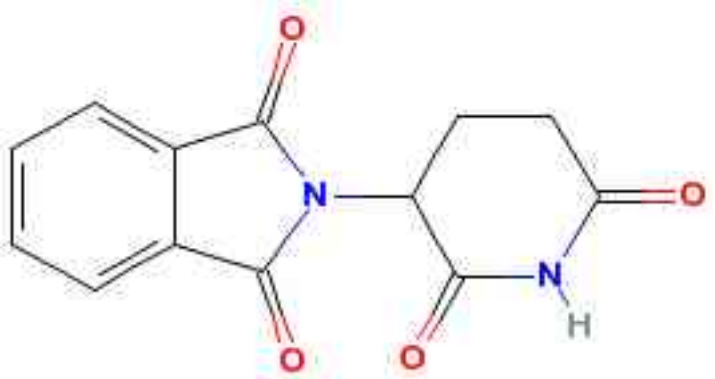
genotypes of parents:	+/*Lx* X +/*Lx*	+/*Lx* X +/*Lx*	+/*Lx* X +/*Lx*
offspring phenotypes:	**25% PD**	**25% PD**	**25% PD**

Examples of human inherited developmental disorders

Teratogenic effect of thalidomide

task 1, page 165

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?

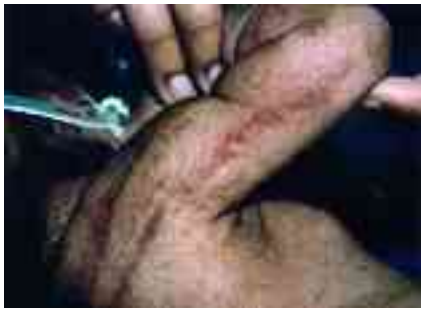
- genetic factors conferring different susceptibility

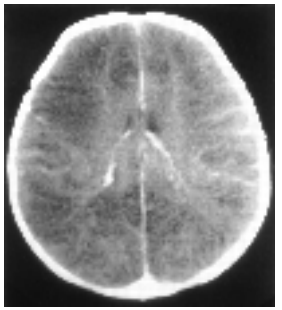
Why was the teratogenic effect not revealed during preclinical testing on rodents?

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

Incontinentia pigmenti (sy. Bloch-Schulzberger)

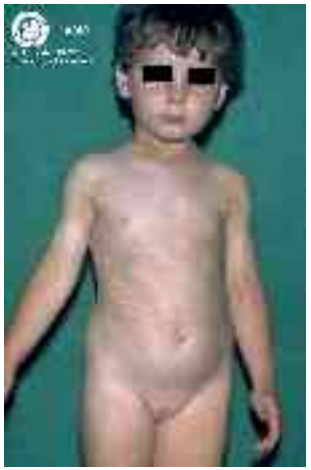
task 2, page 165





- 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

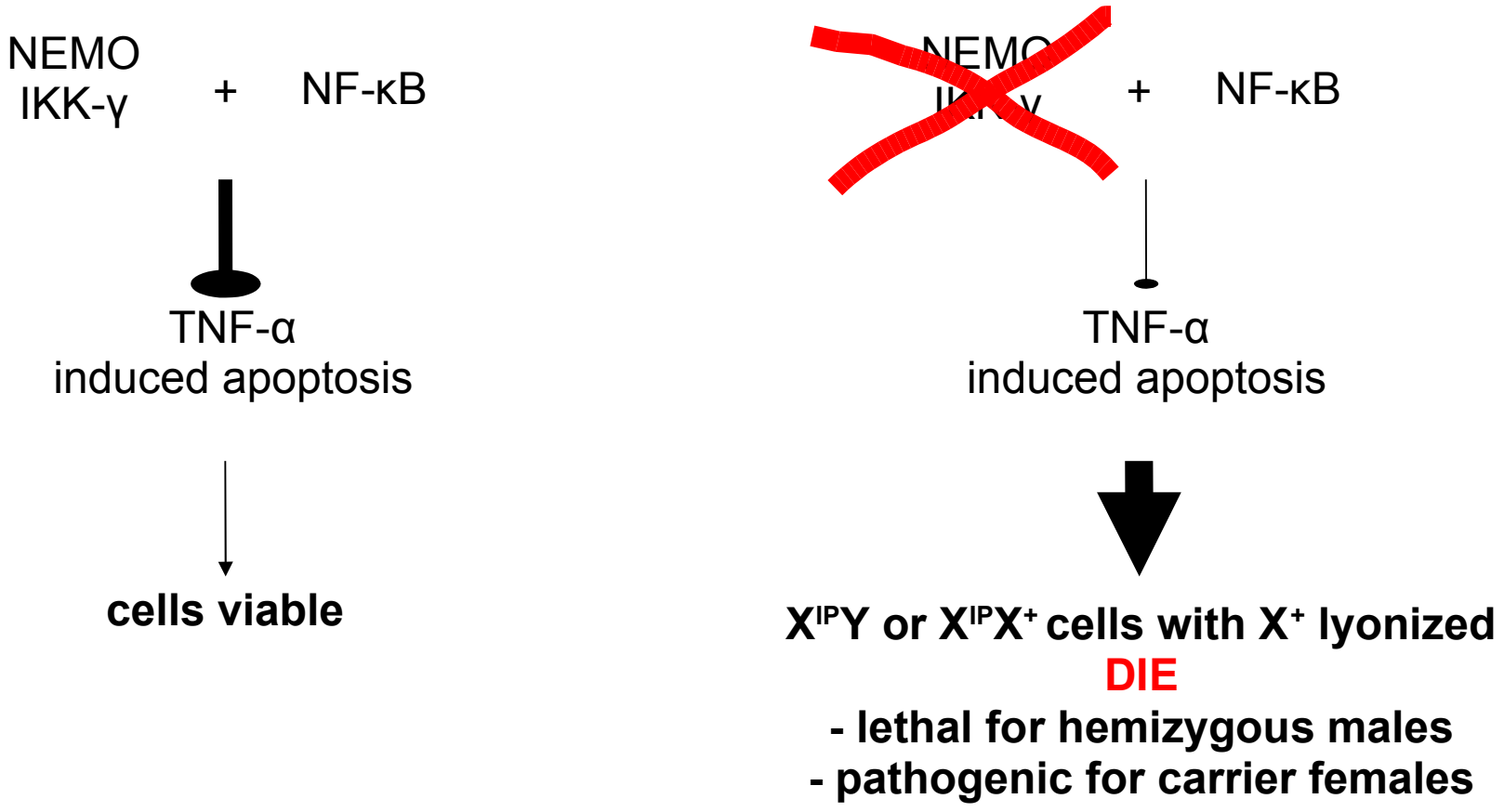
lethal in males

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

Incontinentia pigmenti (sy. Bloch-Schulzberger)

task 2, page 165

Pathogenesis:



Complete androgen insensitivity syndrome

task 3, page 166

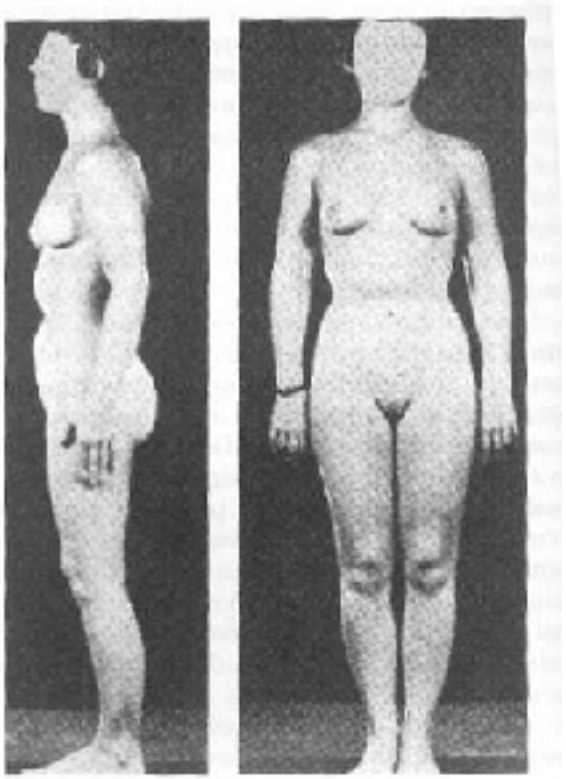
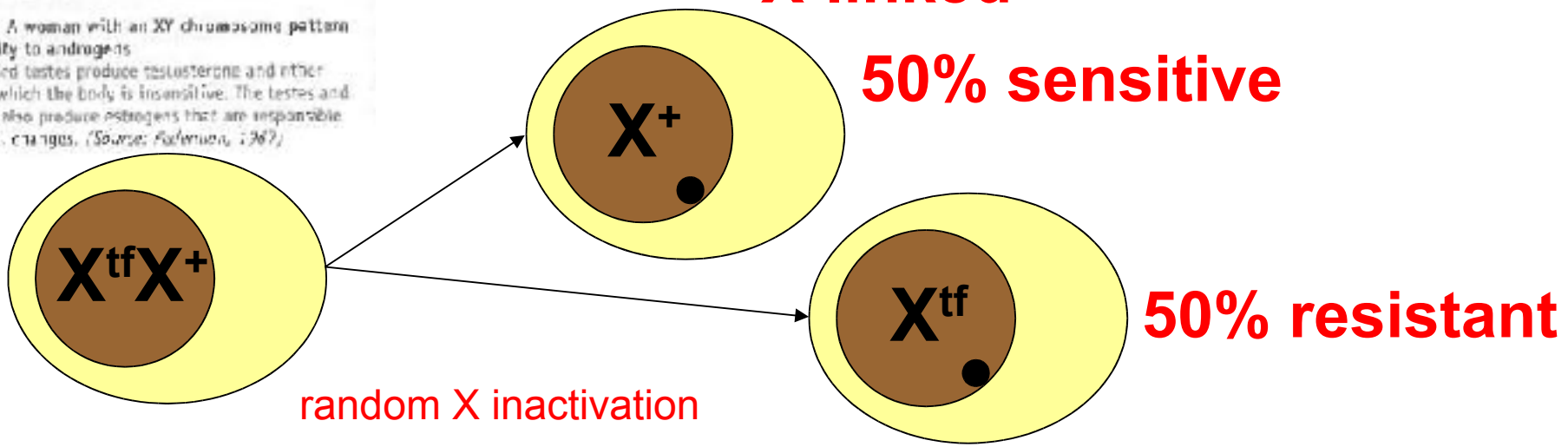


Figure 11.10 A woman with an XY chromosome pattern but insensitivity to androgens
Two undescended testes produce testosterone and other androgens, to which the body is insensitive. The testes and adrenal glands also produce estrogens that are responsible for the puberta. changes. (Source: Fuhrmann, 1967)

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

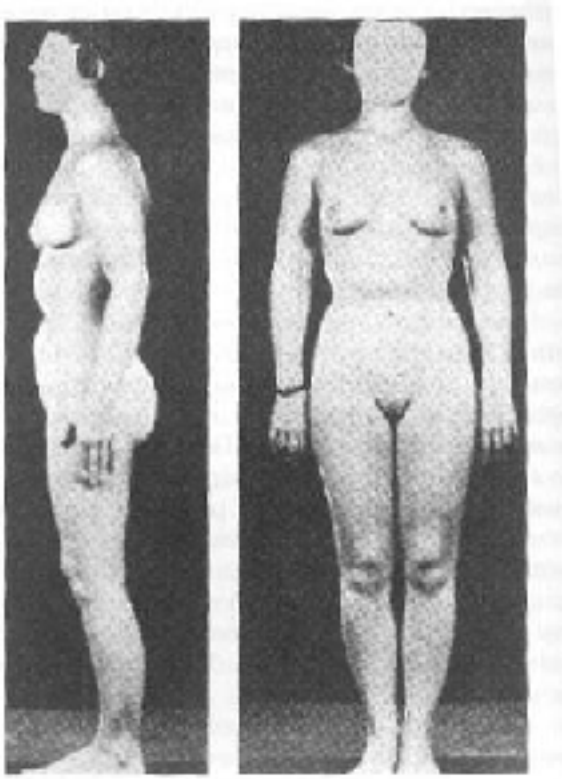
Only 50% cells of the mother sensitive to testosterone - WHY?

X-linked



Complete androgen insensitivity syndrome

task 3, page 166



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  - 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?

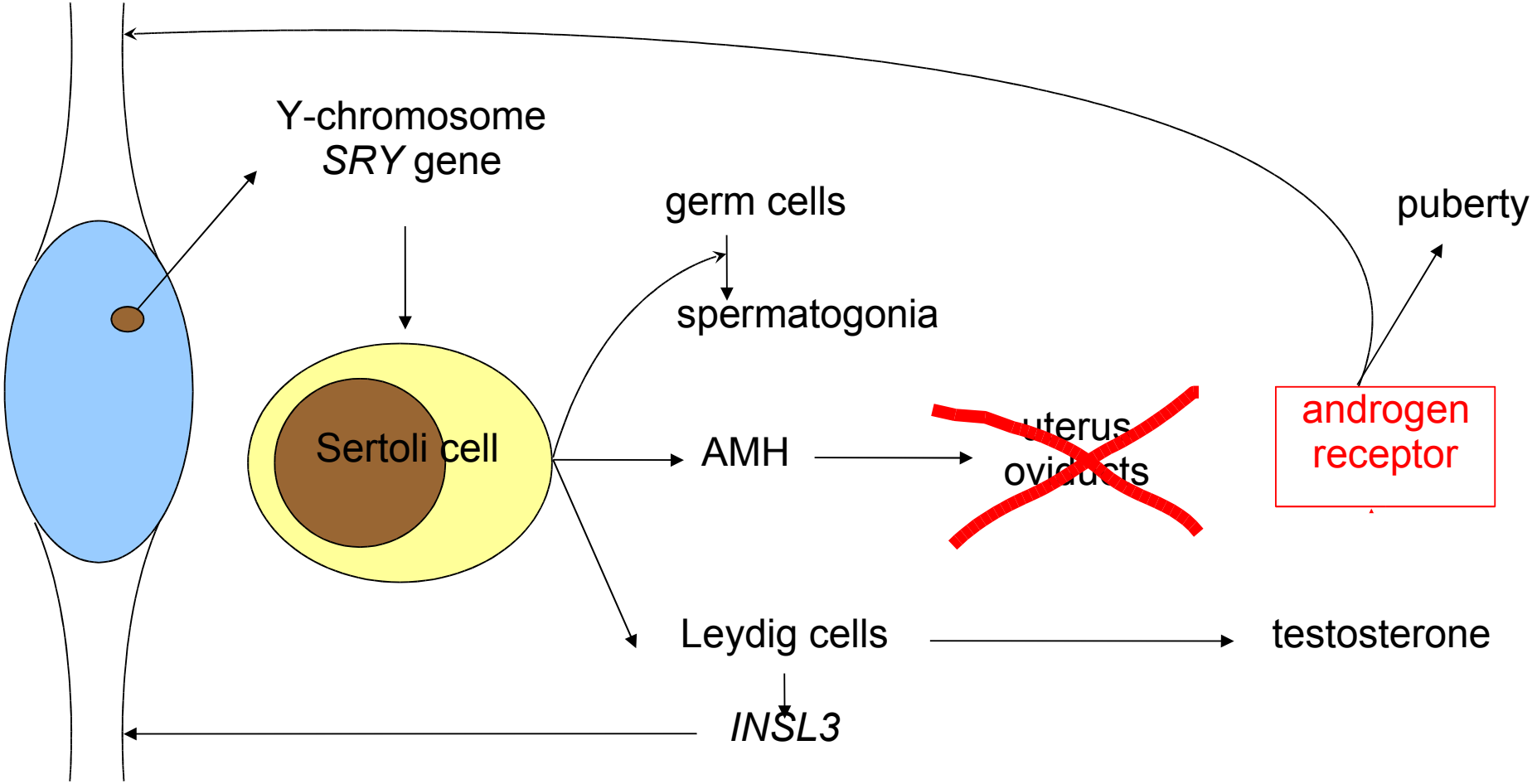
X-linked recessive

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

Complete androgen insensitivity syndrome

task 3, page 166

Why testes develop despite androgen resistance?



gonad differentiation depends on SRY gene on Y chromosome
testosterone is responsible for descent, 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^+
X^+	X^+X^+
X^{eda}	$X^{eda}X^+$

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

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)

Anhidrotic ectodermal dysplasia is caused by mutation of *EDA* gene

This gene codes for a protein ectodysplasin, member of TNF family proteins, that is a signaling molecule in epithelium morphogenesis and patterning