Genetics = the study of *heredity*

***Genes* = the "matter" of heredity**

Pythagoras (580-500 B.C.):

Hereditary material present as a cocktail in semen --
fluids collected from every organ as it travels through body.

But, how to account for obvious shared physical traits between mother and offspring?!

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Empedocles (490-430 B.C.):

Hereditary material in *both* semen *and* female sexual fluid -- embryo results from mixture of the two.

‘They were poured in pure places; some met with cold and became women’
‘For the male was warmer . . . this is the reason why men are dark, more powerfully built, and hairier’.

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Aristotle (384-322 B.C.):

Inheritance = physical substance coming from both parents

Semen = man's purified blood --
engenders child when comingled with woman's menstrual blood

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

William Harvey (1578-1657):

Blood does NOT contribute to formation of fetus --
questioned direct role of semen in inheritance.

Egg fertilized inside female by some kind of infection begun by sexual act!

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Antonie van Leeuwenhoek (1632-1723):

Living things generated by cellular interactions.

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

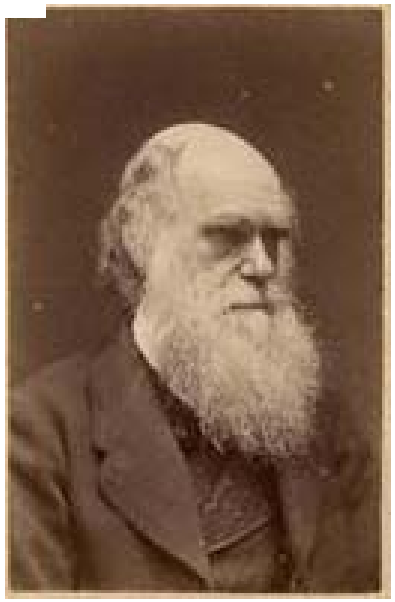
Pierre-Louis Moreau de Maupertuis (1698-1759):

First to study inheritance pattern of human disorder in single family -- anticipated modern idea of dominant/recessive genes.

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Charles Darwin (1809-1882):

Pangenesis: small particles produced throughout body flow through bloodstream.



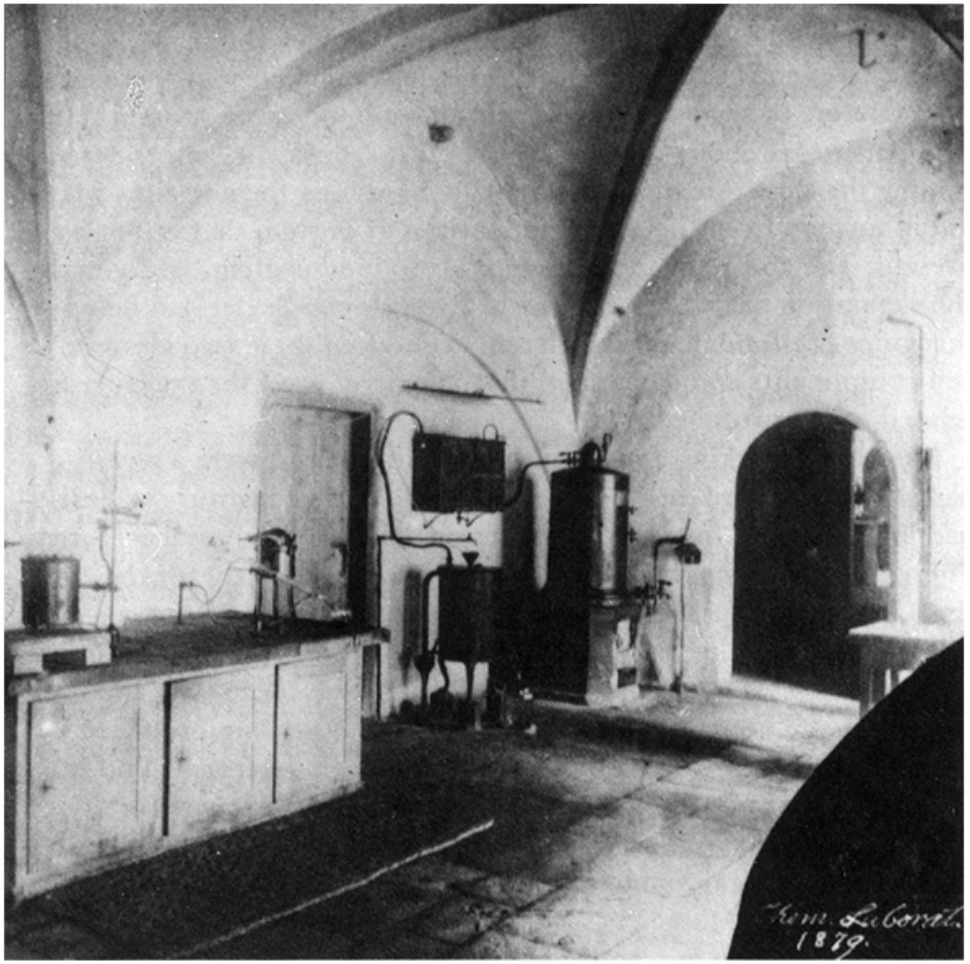

Pen & Ink Sketches N°7
A CHIP OF THE OLD BLOCK.
My gracious! here's a likeness,— why it's Daddy all over bless its little soul.


Gregor Mendel.
Um das Jahr 1862.

Gregor Mendel (1822-1884)

<u>Experiments in Plant Hybridization</u> 1865

“differentiating characters”



Friedrich Miescher

1869:
nuclein (DNA) from pus

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

Thomas Hunt Morgan (1866-1945)

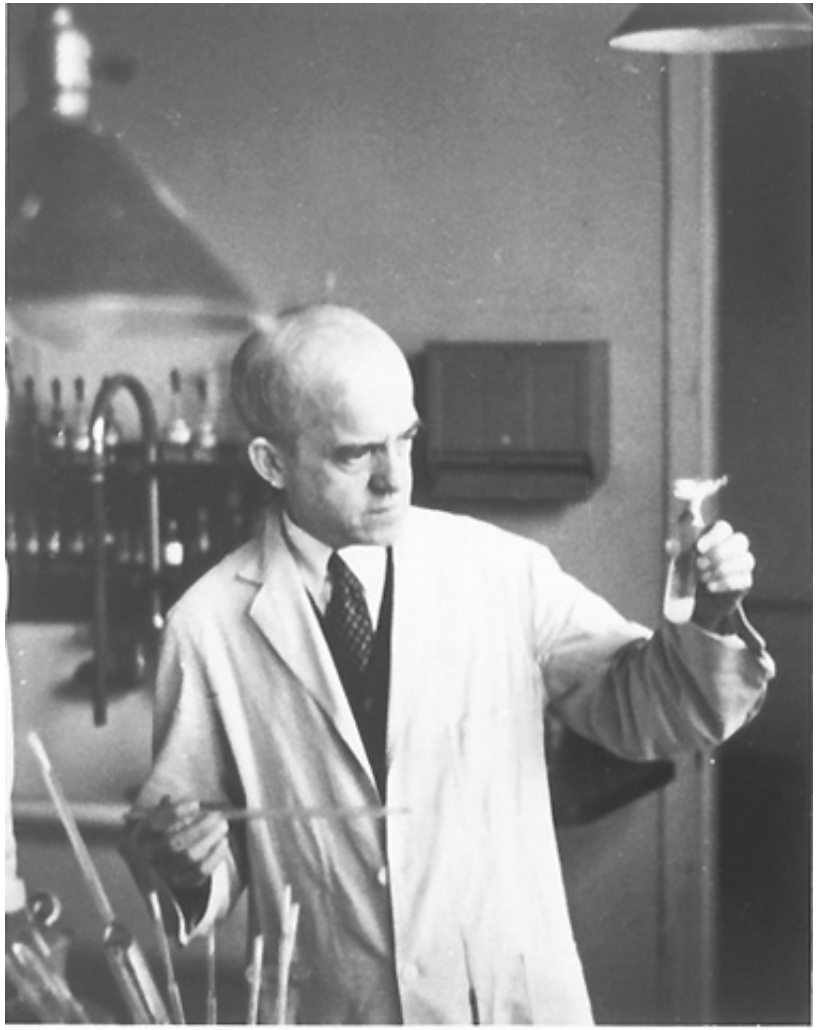
Heredity is based on genes carried on chromosomes.

1933 Nobel Prize:

Discovery of hereditary transmission mechanics in *Drosophila*

“The fittest family”

Eugenics Record Office: “breeding” better humans



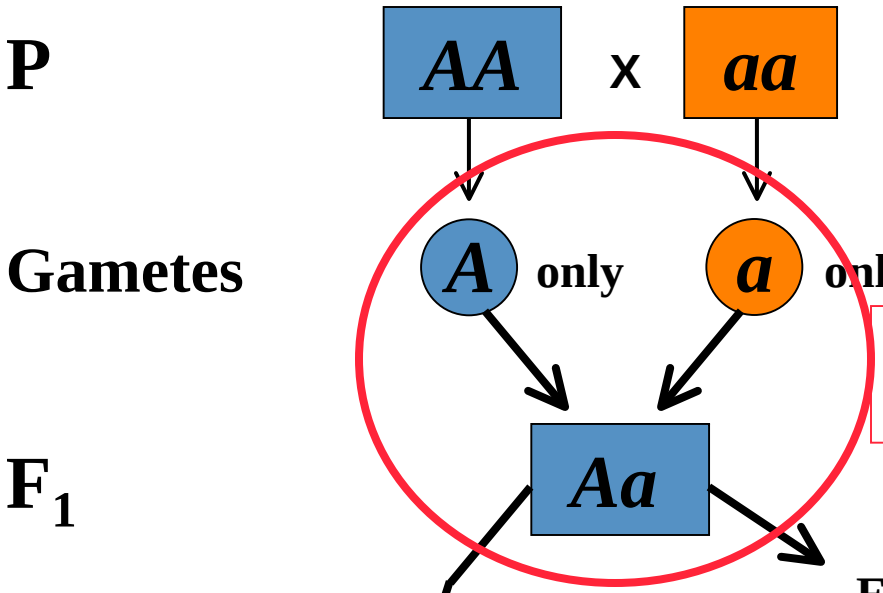
Oswald Avery, Colin Macleod, Maclyn McCarty

1940’s

gene = DNA

Watson & Crick, 1953

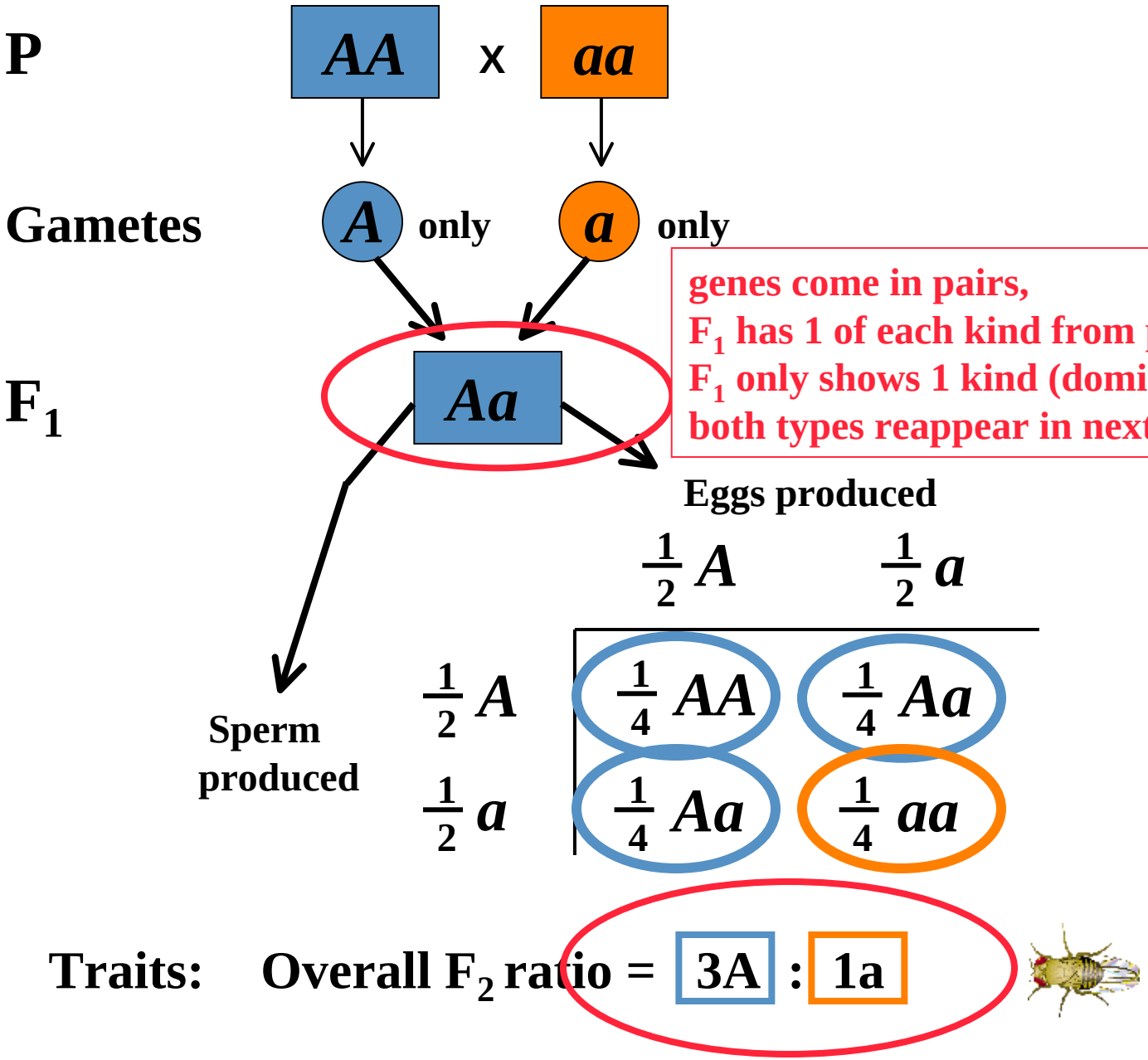

THAT'S ONE SMALL STEP FOR MAN,...

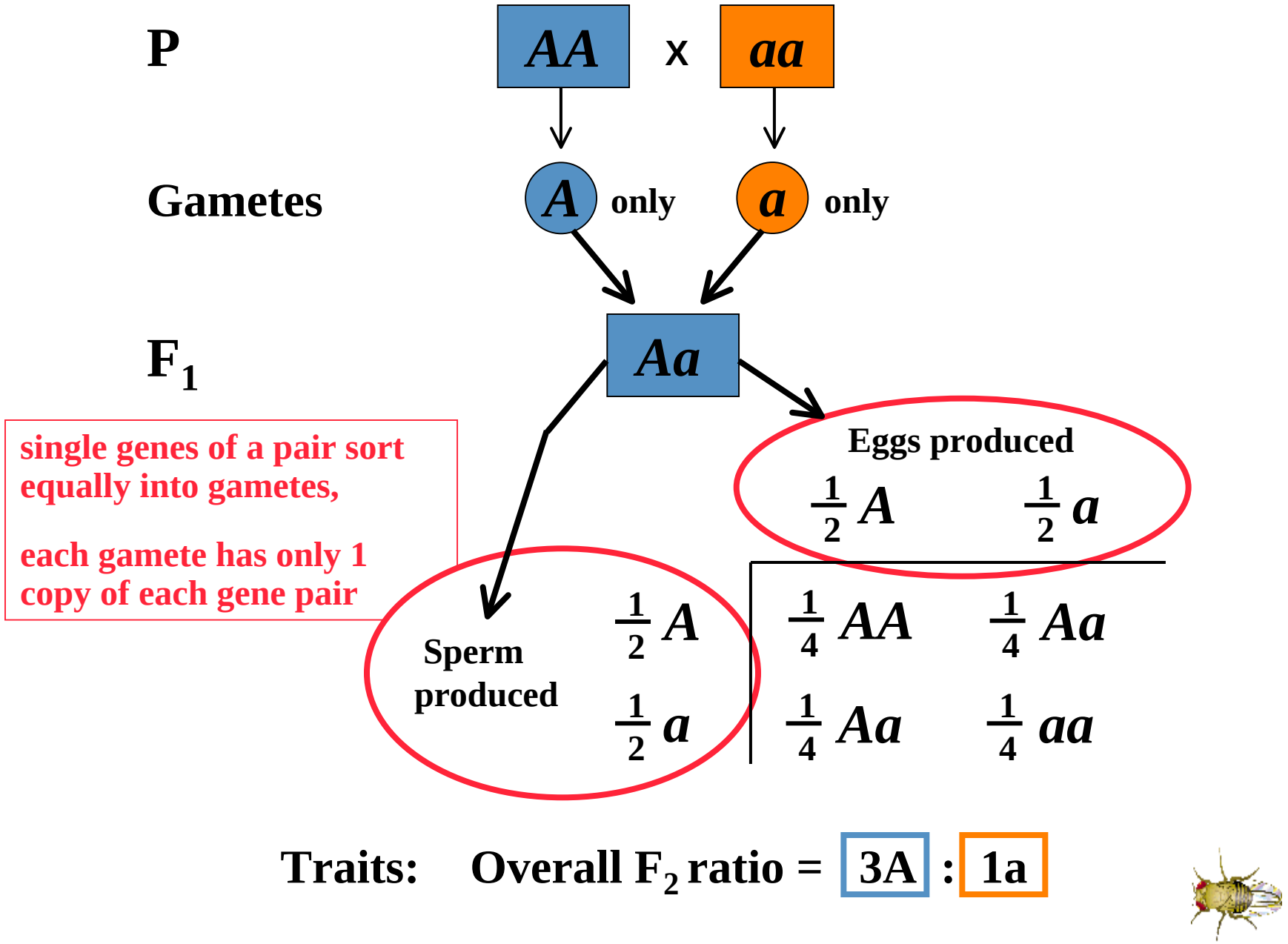


hereditary determinants are particulate (no blending)

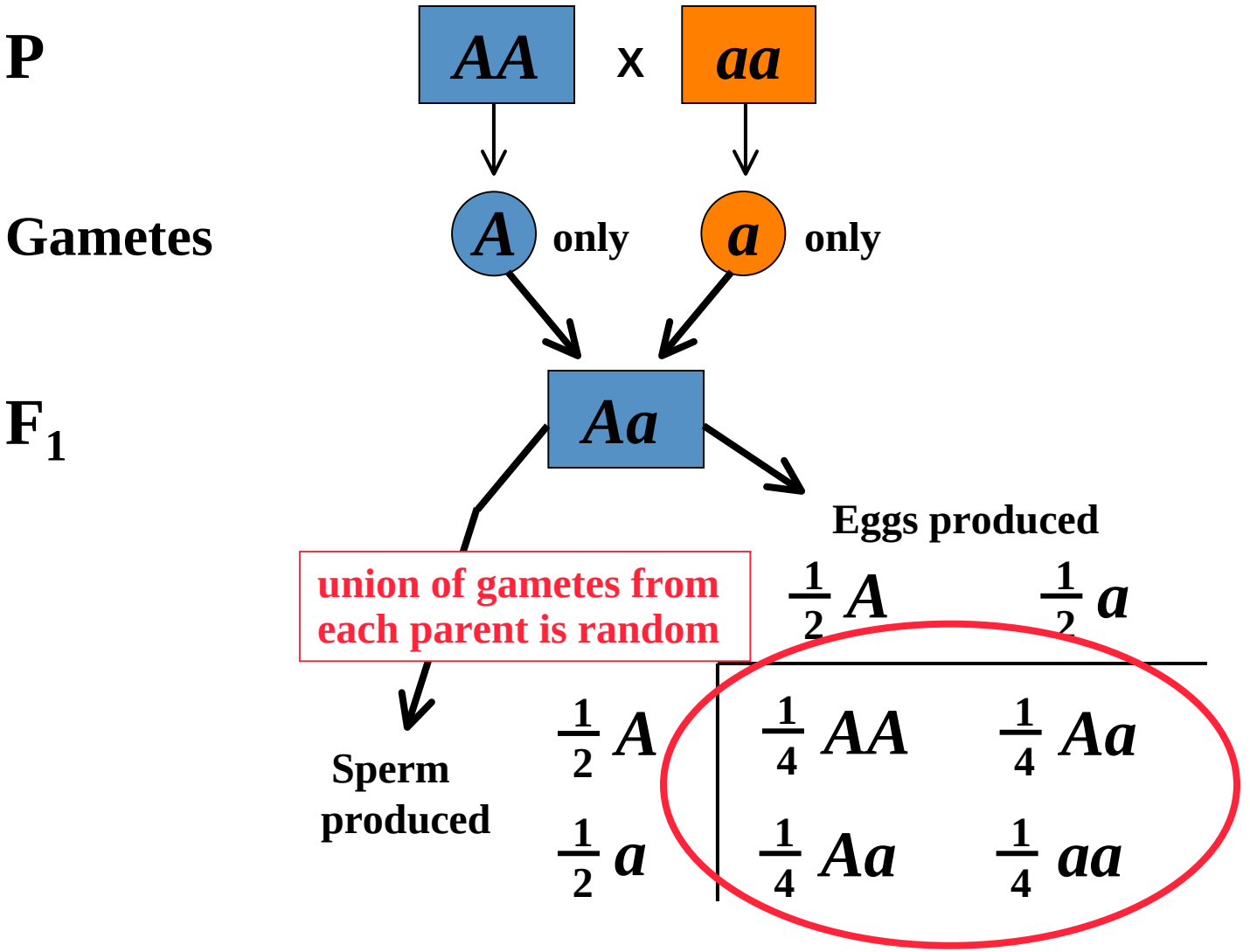
Sperm produced	Eggs produced: $\frac{1}{2}A$	Eggs produced: $\frac{1}{2}a$
$\frac{1}{2}A$	$\frac{1}{4}AA$	$\frac{1}{4}Aa$
$\frac{1}{2}a$	$\frac{1}{4}Aa$	$\frac{1}{4}aa$

Traits: Overall F_2 ratio = **3A : 1a**


P
AA
x
aa
Gametes
A only
a only
F1
Aa
genes come in pairs,
F1 has 1 of each kind from parents,
F1 only shows 1 kind (dominant),
both types reappear in next generation
Eggs produced
1/2 A
1/2 a
Sperm produced
1/2 A
1/2 a
1/4 AA
1/4 Aa
1/4 Aa
1/4 aa
Traits: Overall F2 ratio = 3A : 1a

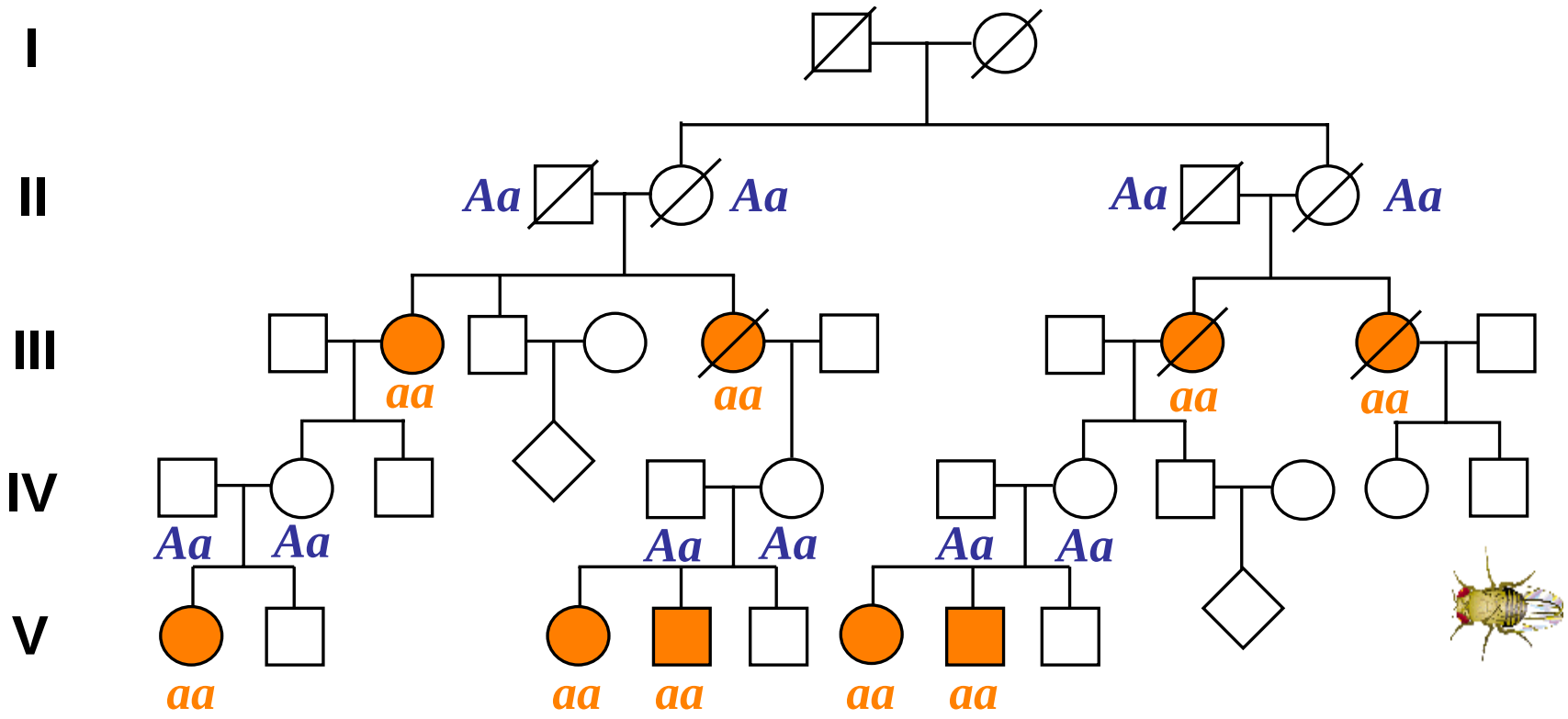


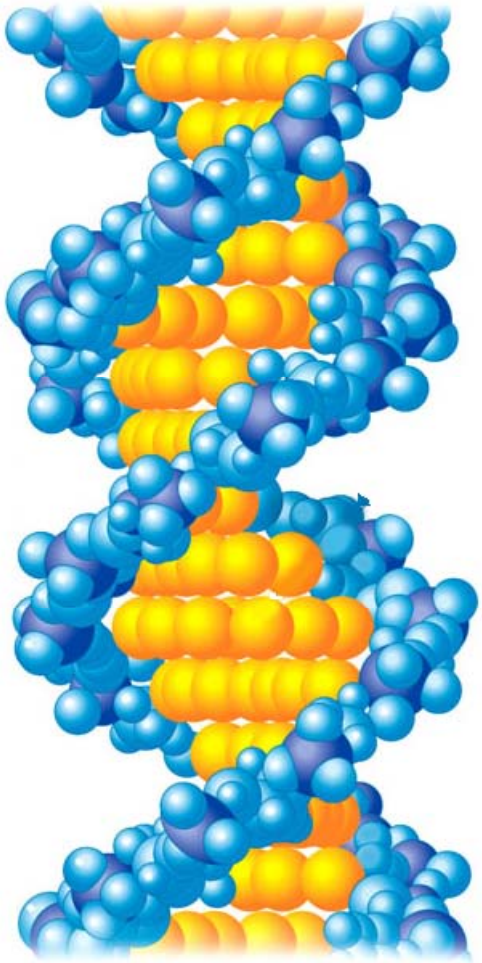
Traits: Overall F_2 ratio = **3A** : **1a**

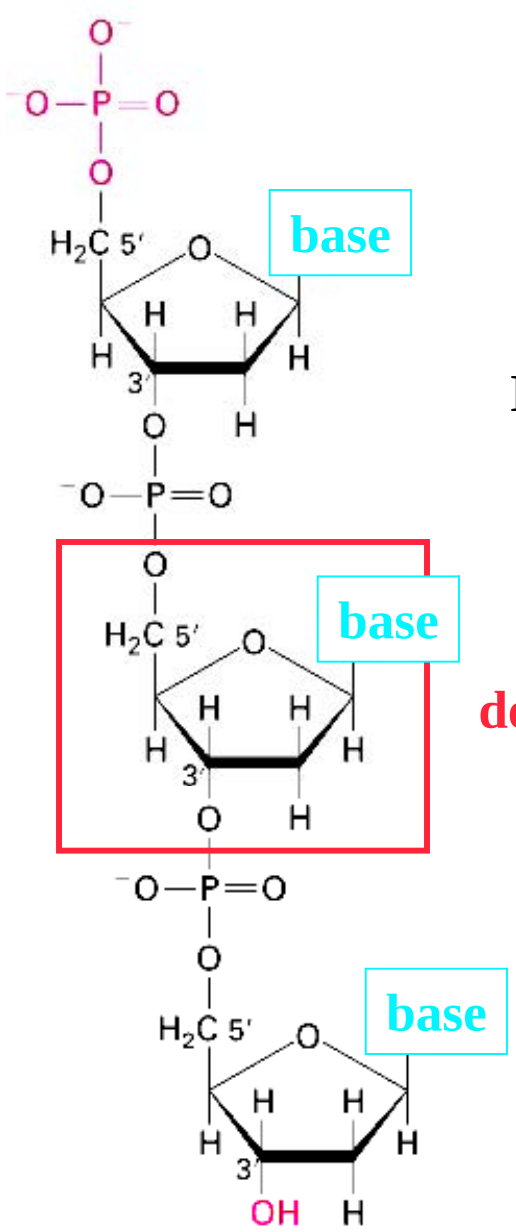


Traits: **Overall F_2 ratio =** **3A** : **1a**

Autosomal Recessive Inheritance







DNA sugar-phosphate backbone

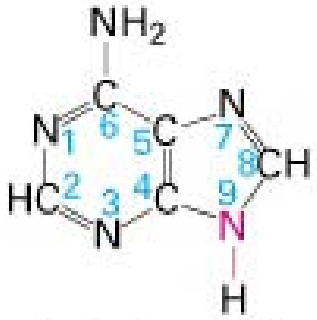
deoxyribose

(deoxy*ribo*nucleic acid)

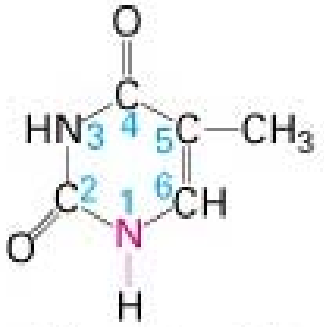
DNA bases

PURINES

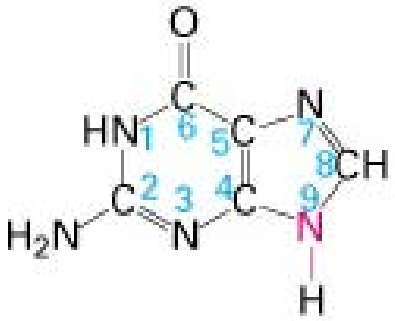
PYRIMIDINES



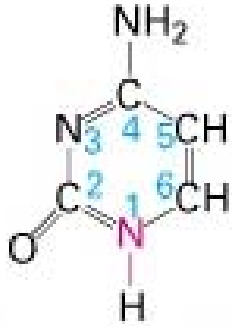
Adenine (A)



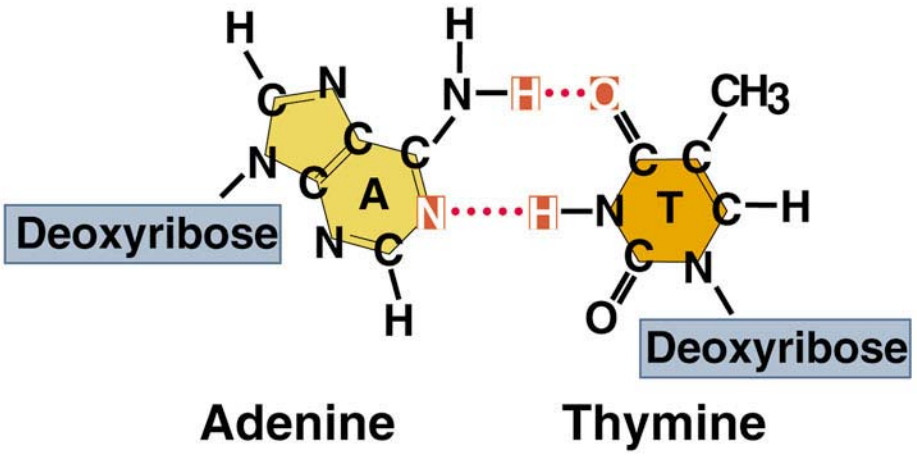
Thymine (T)



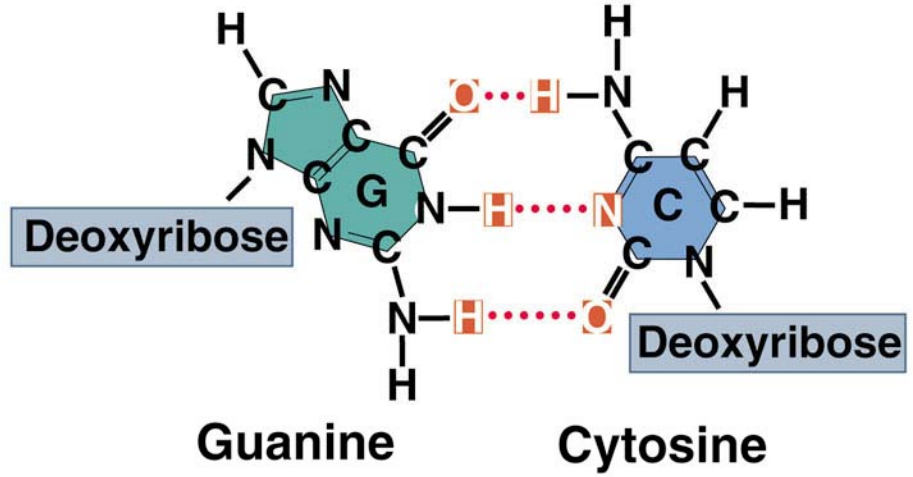
Guanine (G)



Cytosine (C)

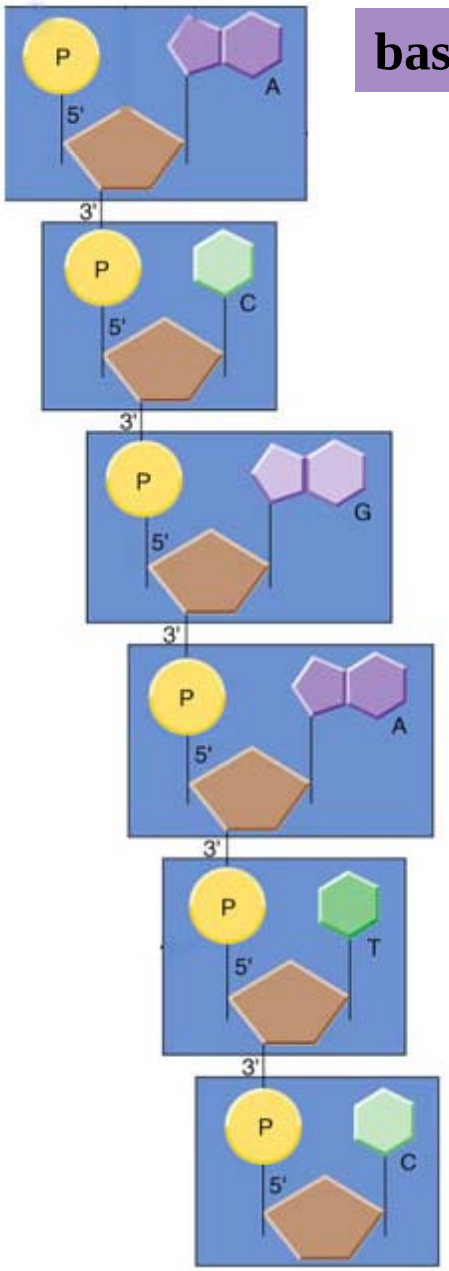


DNA base pairing



phosphate

sugar



base

DNA polymer

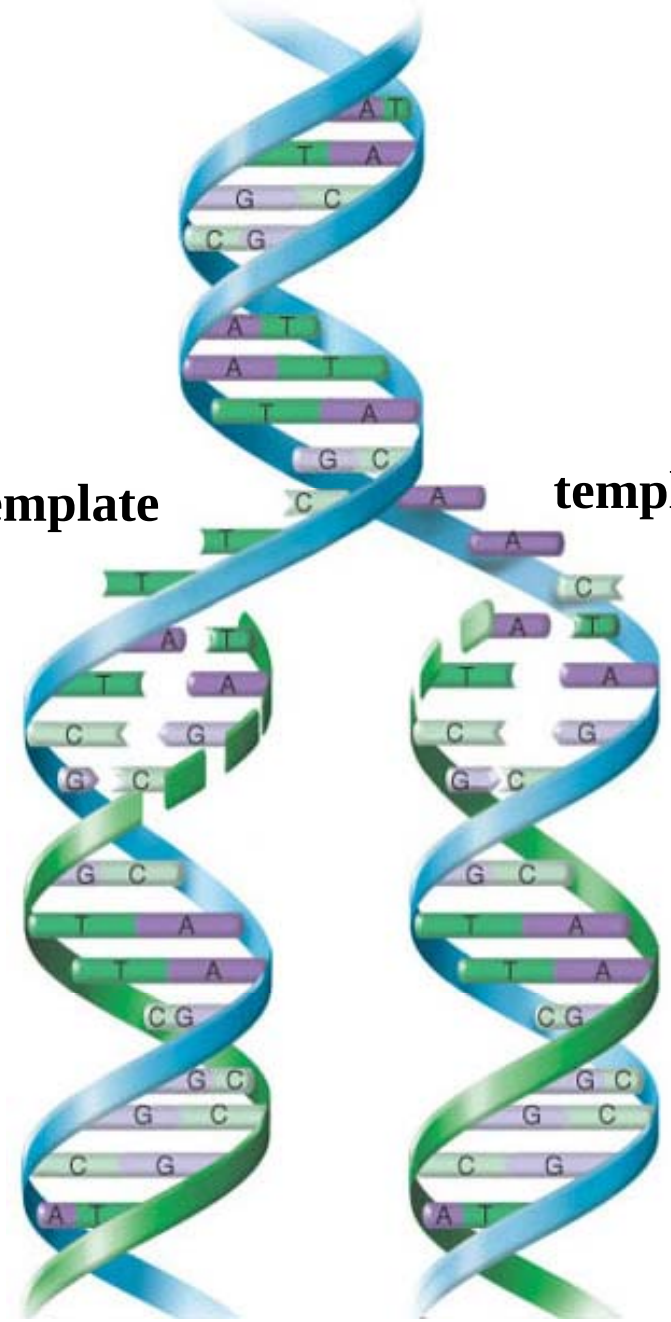
(nucleotide polymer)

QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

replicating DNA

template

template



daughter helices

The Central Dogma

DNA

↓

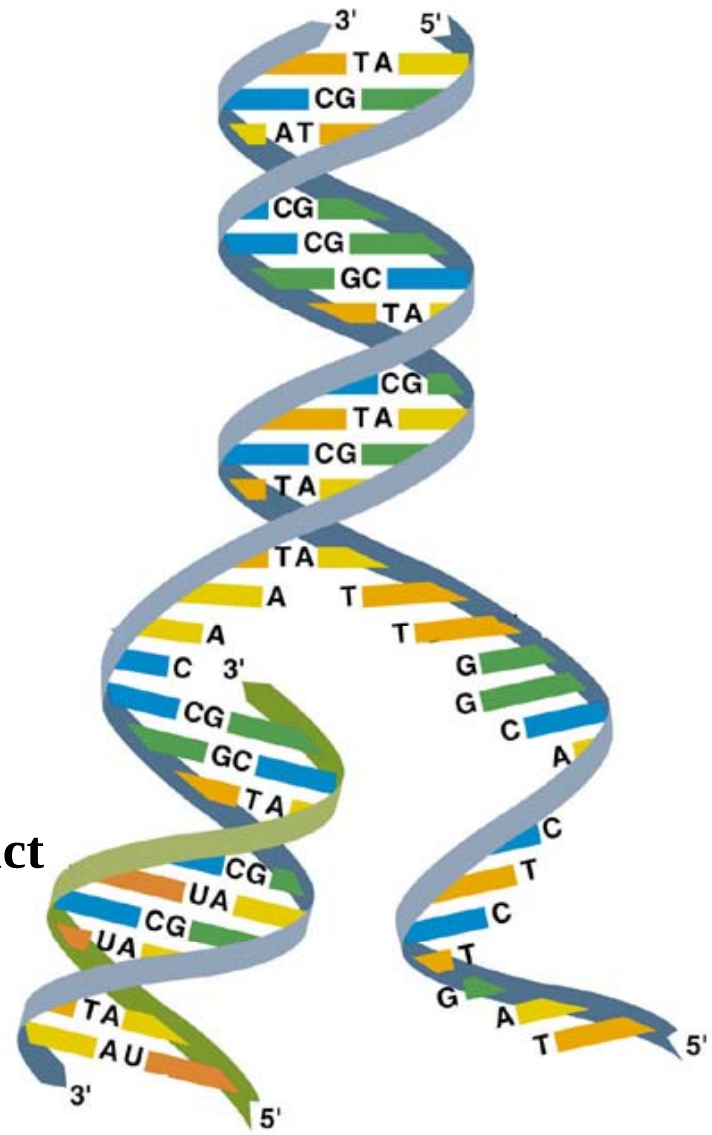
RNA (***ribo*nucleic acid)**

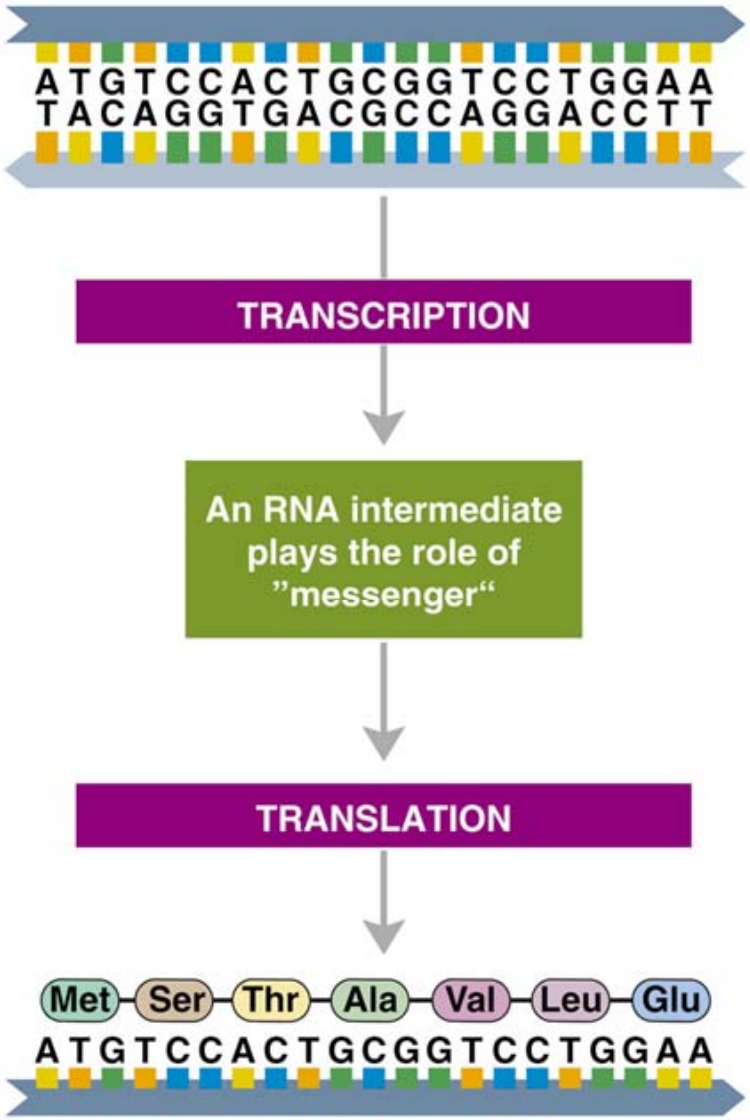
↓

protein

DNA being transcribed

RNA product





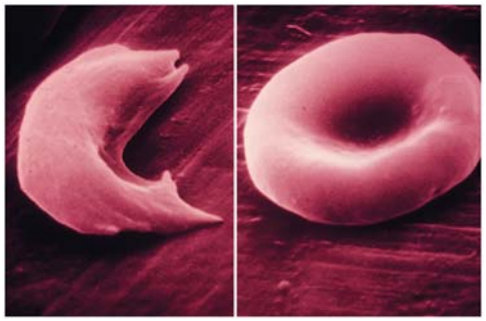
DNA

protein

RNA

the Genetic Code

First letter	Second letter: U	Second letter: C	Second letter: A	Second letter: G	Third letter
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G



sickle cell rbc

normal rbc

defective gene: mutant hemoglobin

normal DNA	GTG CAC CTG ACT CCT **GAG** GAG AAG TCT
sickle cell DNA	GTG CAC CTG ACT CCT **GTG** GAG AAG TCT

normal Hb	VAL HIS LEU THR PRO **GLU** GLU LYS SER
sickle cell Hb	VAL HIS LEU THR PRO **VAL** GLU LYS SER

Genetic Diagnosis

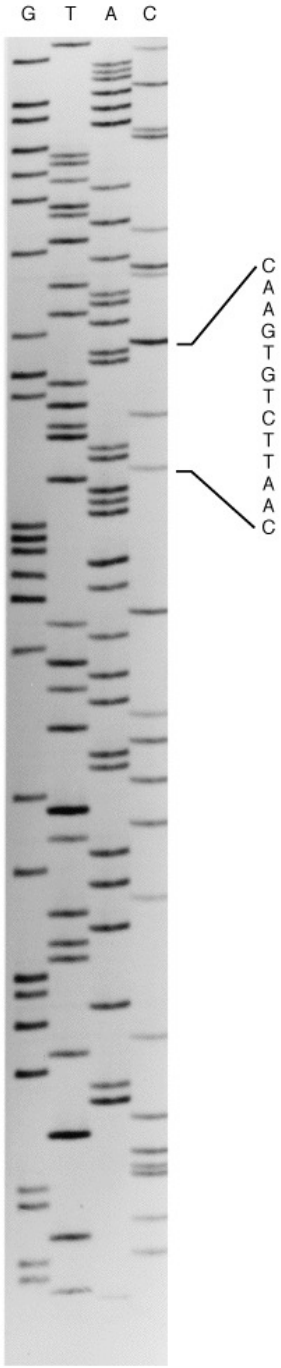
Functional/structural assays of proteins (genetic endproducts)

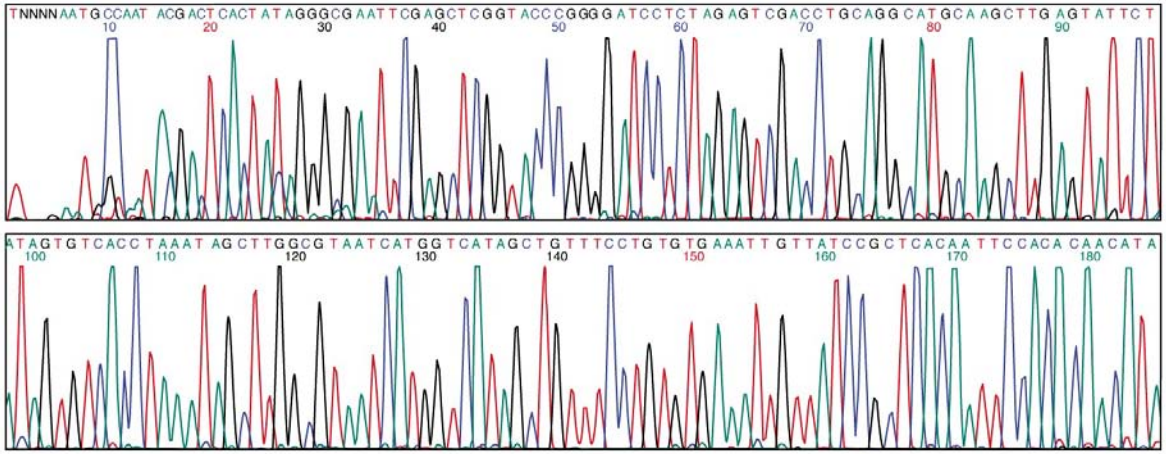
e.g.:

- **newborn screening for inherited metobolic diseases**
  [phenylketonuria: phenylalanine hydroxylase]
- **detection of variant hemoglobin form: sickle cell anemia**

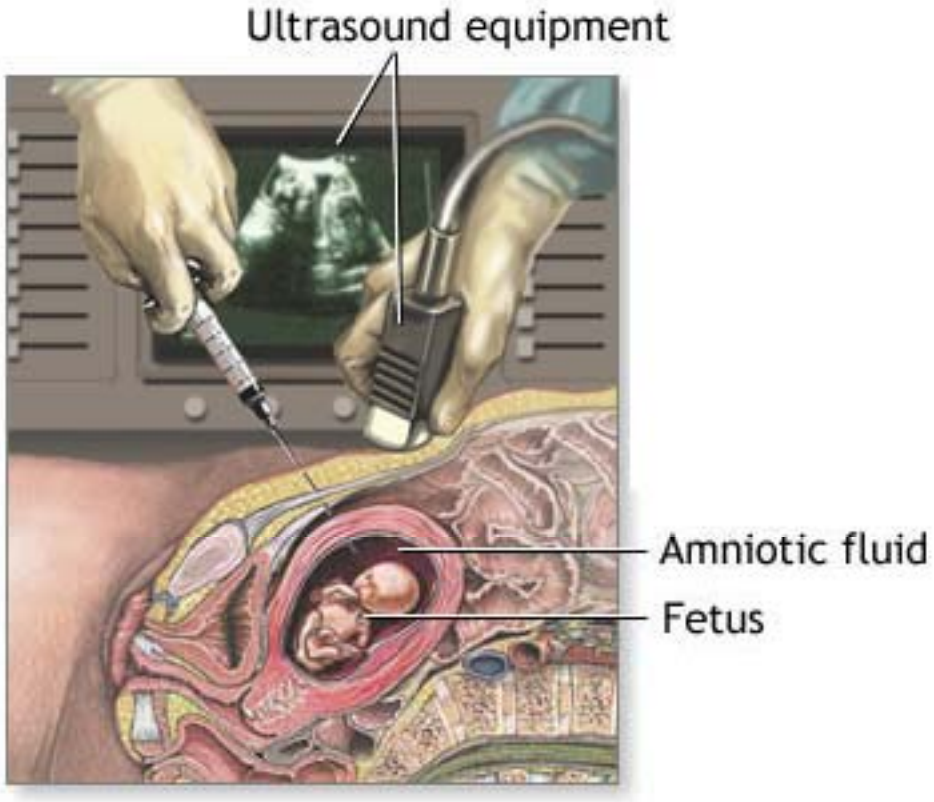
Direct analysis of DNA

DNA sequence analysis



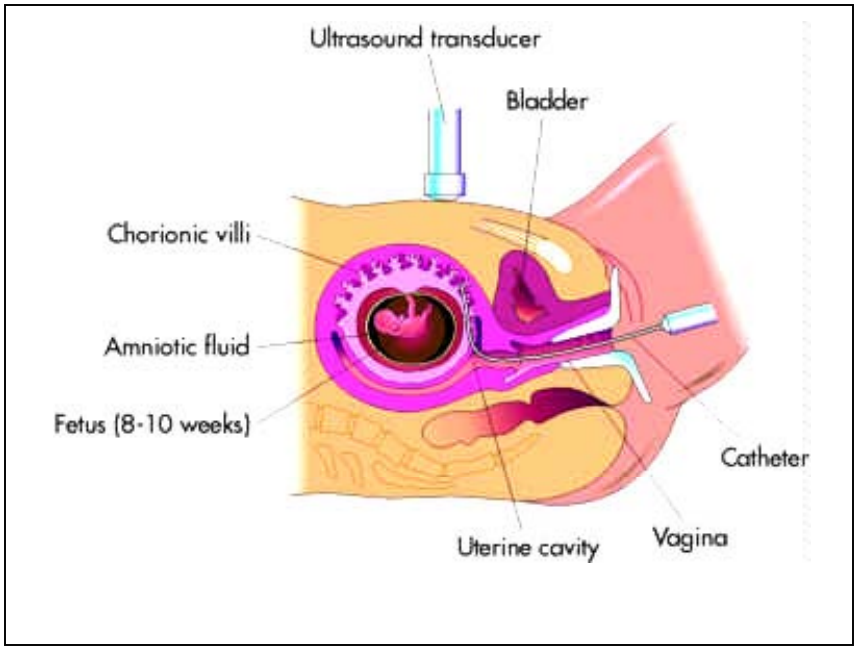


postimplantation genetic diagnosis



amniocentesis

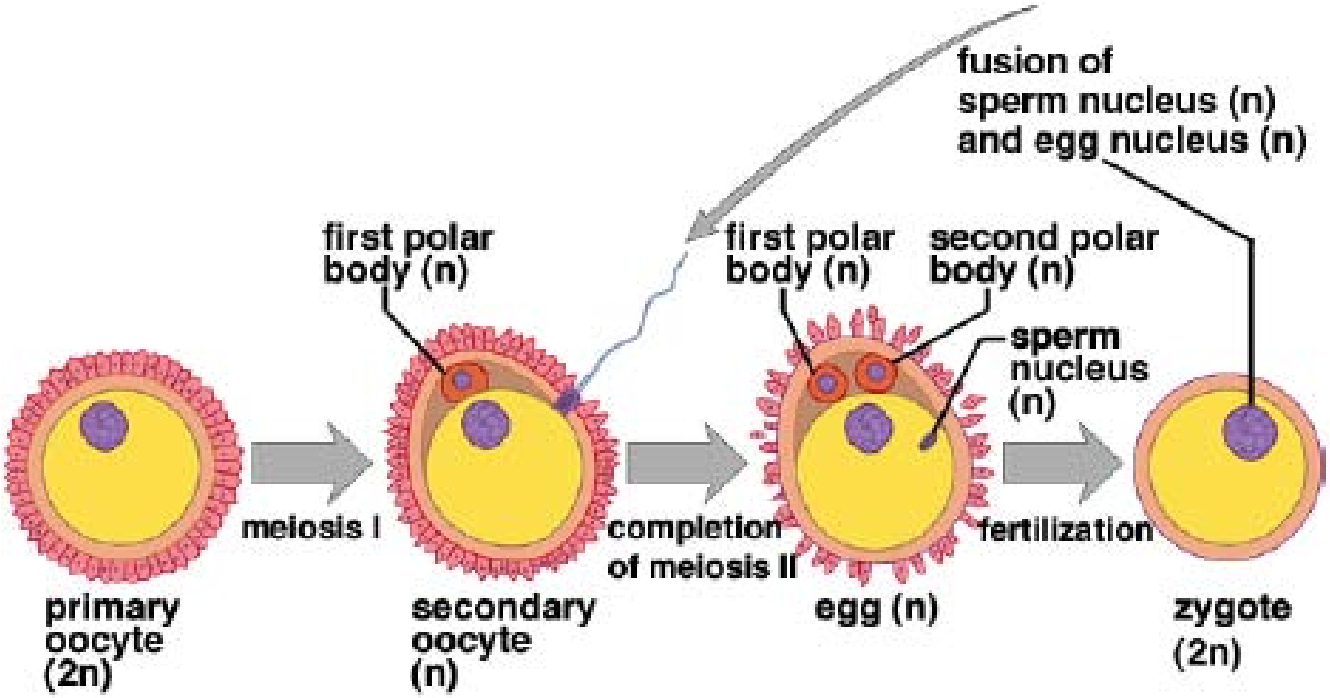
chorionic villus sampling (CVS)



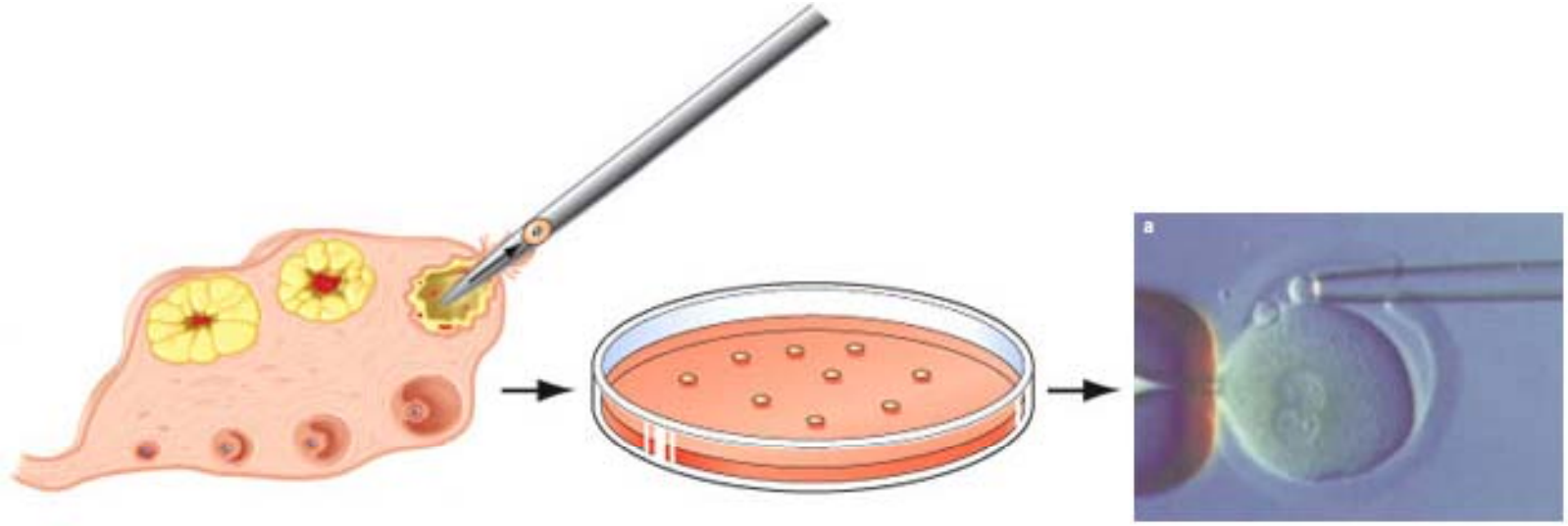
preimplantation genetic diagnosis (PGD)

***in vitro* fertilization (IVF) followed by biopsy**

oogenesis & fertilization



polar body diagnosis



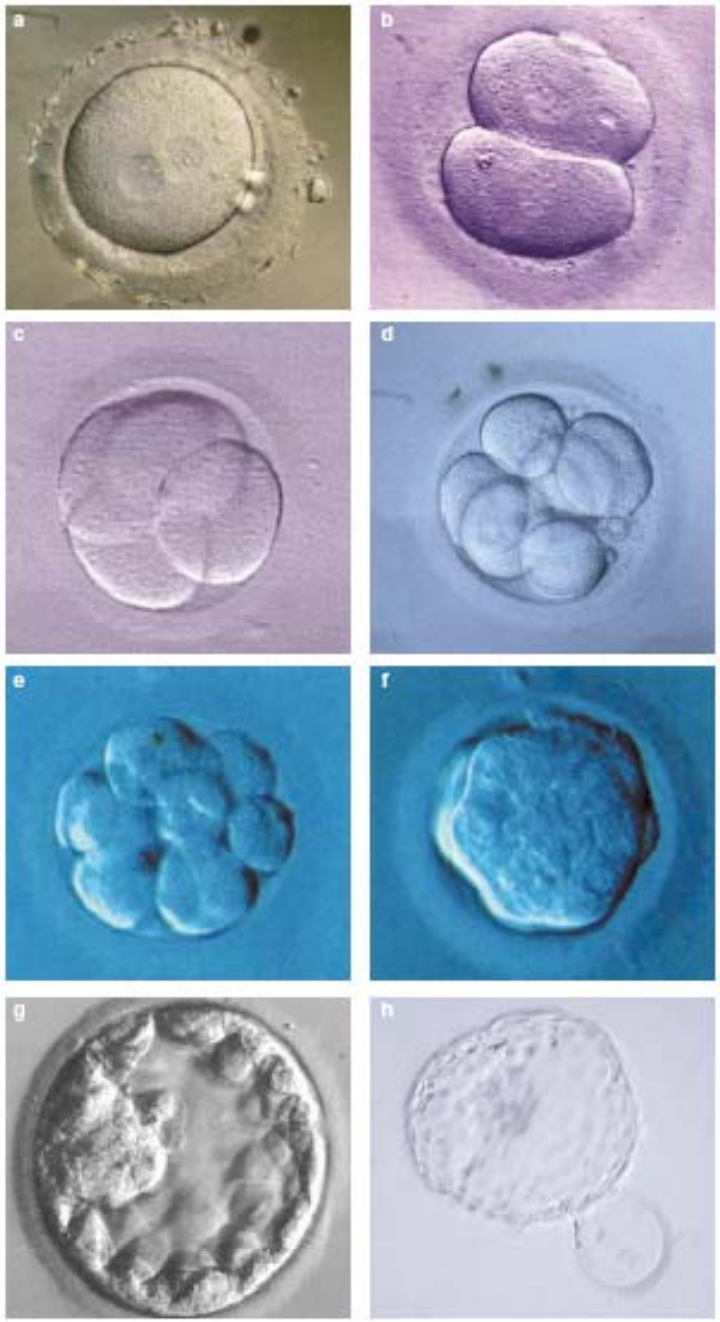
collect mature eggs

fertilize with sperm

20-30 hrs later > remove polar body & test

- infer embryo's genetic condition without risk of damage, BUT
- cannot learn about paternal contribution

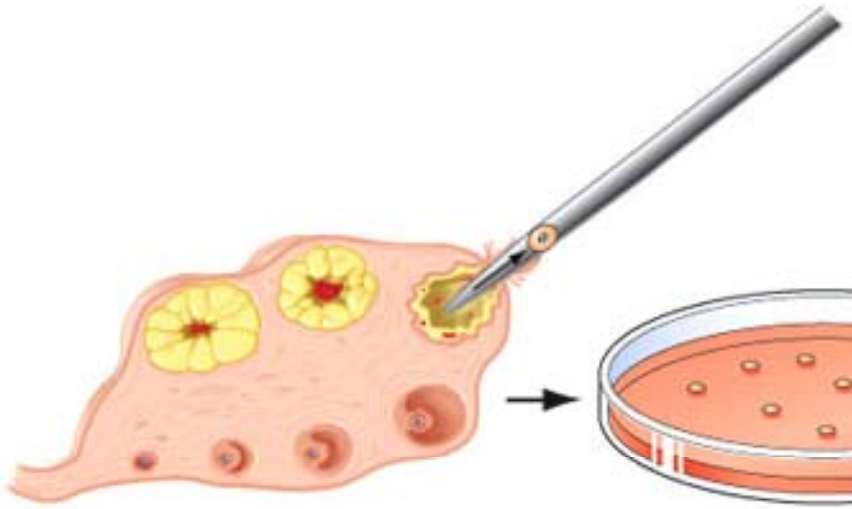
zygote

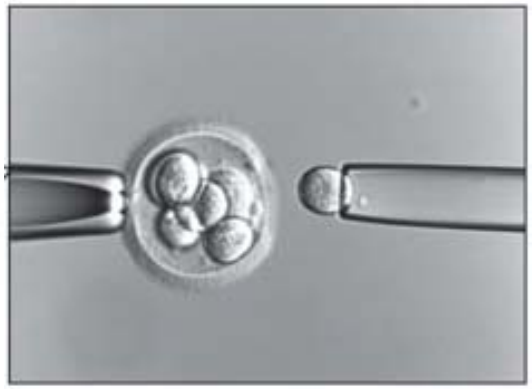


preimplantation development

0 through 6 days post fertilization

cleavage stage diagnosis

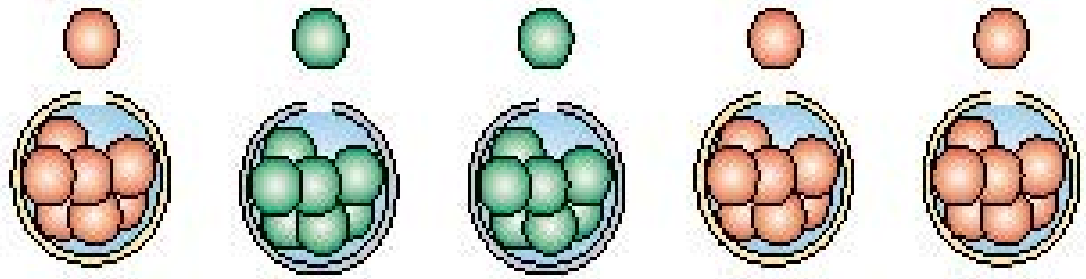




collect mature eggs

fertilize with sperm

at 6-10 cell stage, 1 cell removed from each embryo to test



- **assess BOTH maternal & paternal genetic contributions**
- **direct assessment = more reliable, BUT some risk of damage to embryo**

Gene Therapy

= the treatment of disease by genetic modification of patient's cells

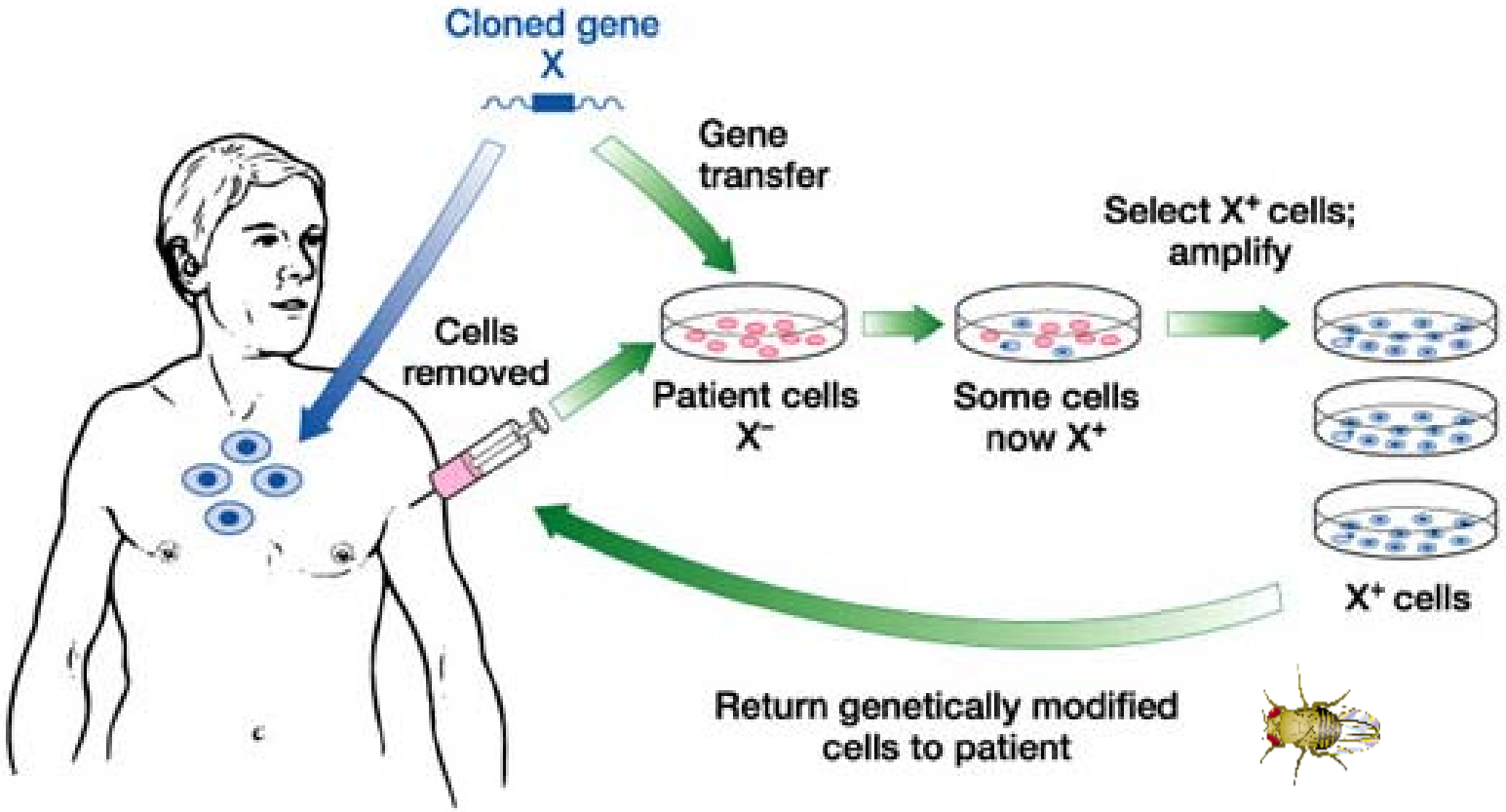
Gene Therapy “needs”

- **appropriate target cell with long half-life or good replicative potential *in vivo***
- **technical strategy to carry/transfer corrective gene into target**

Target Cells

- **appropriate tissue type**
- **easily accessible**
- **long life span**
- **proliferating, if delivery vector needs to integrate into replicating DNA**

stem cells: totipotent embryonic vs. multipotent/restricted adult

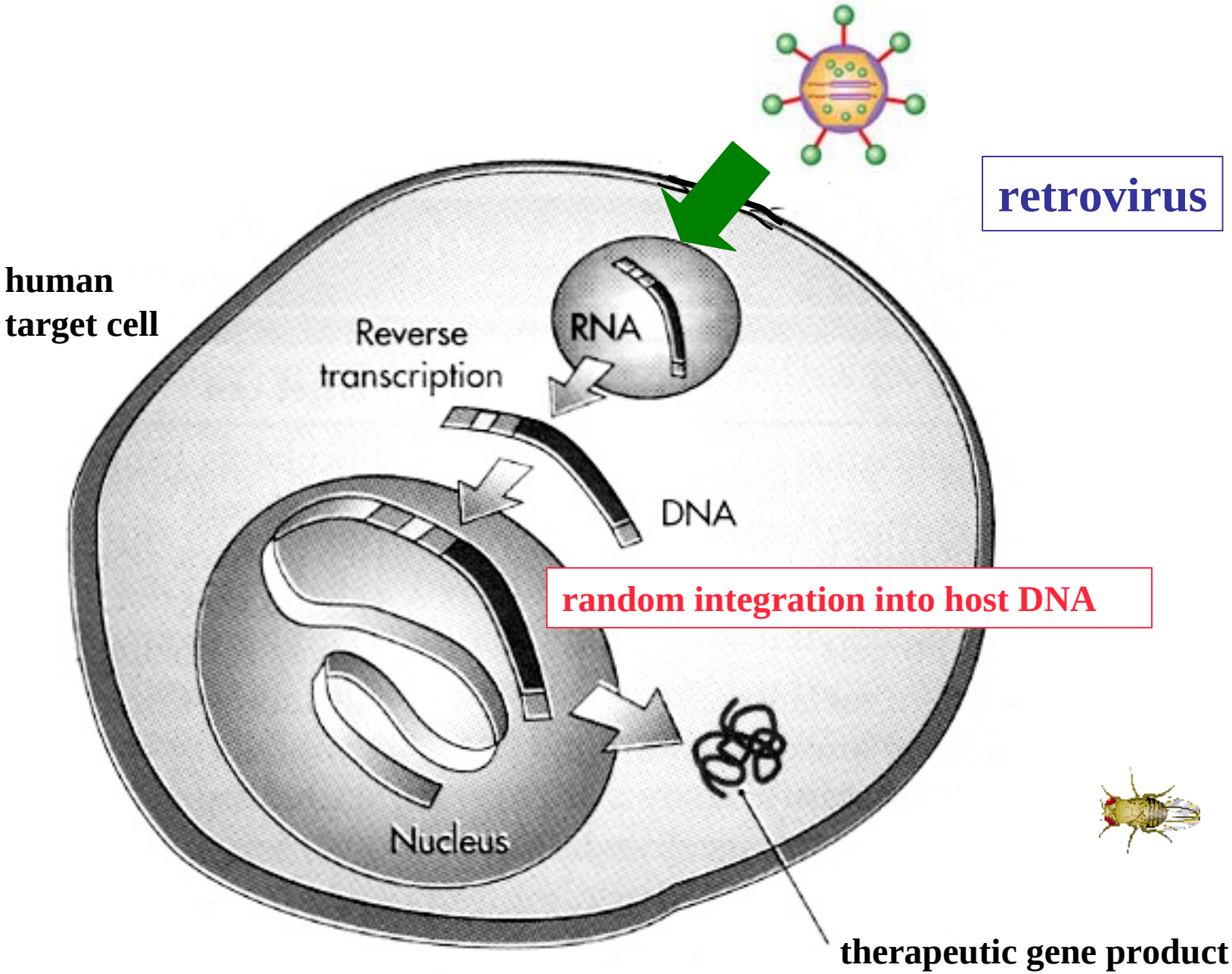


***in vivo* gene therapy**

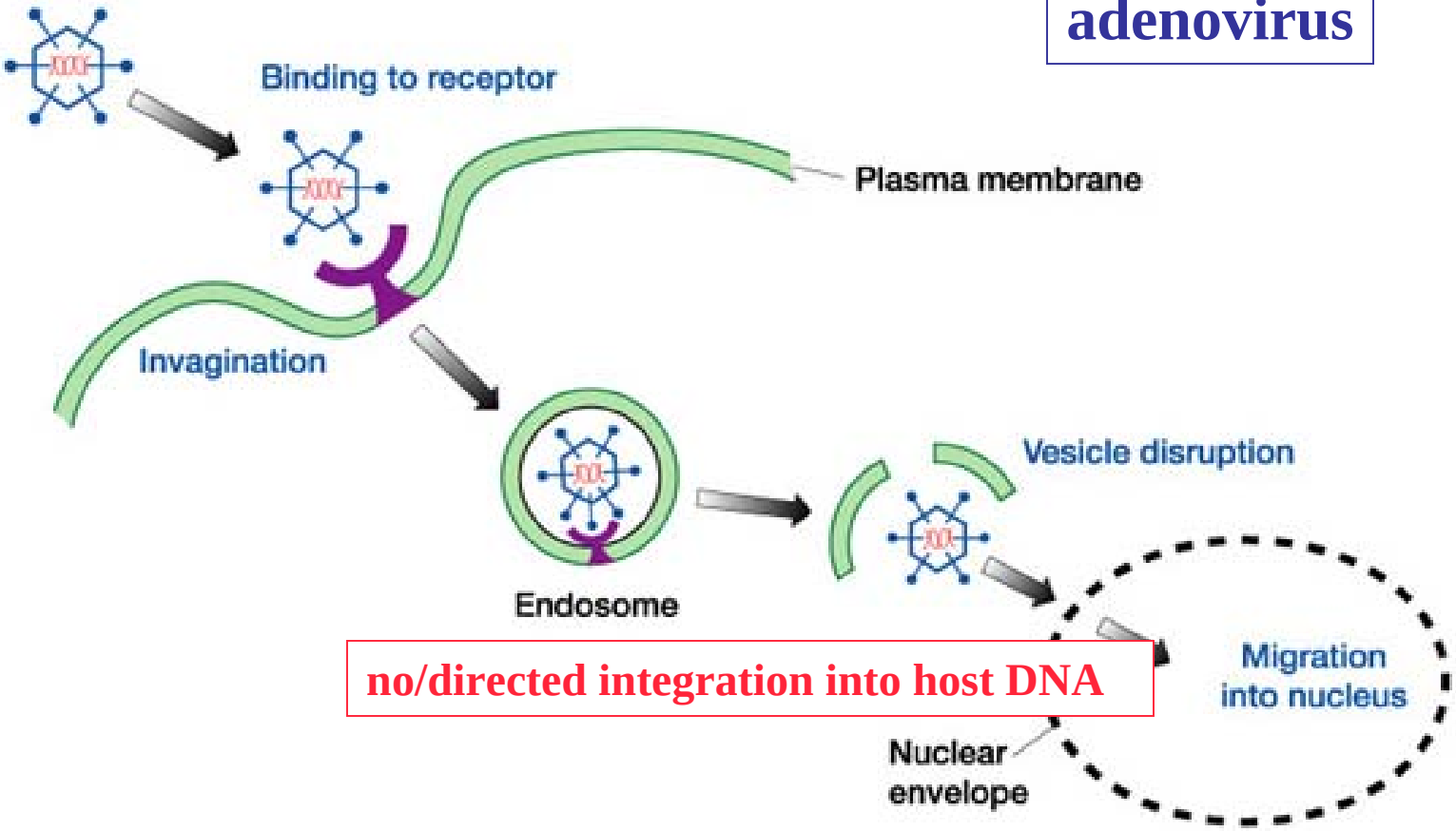
***ex vivo* gene therapy**

Strategies for introducing genes into cells:

- **cell fusion**
- **calcium phosphate coprecipitation**
- **microinjection**
- **electroporation**
- **liposome fusion**
- **direct introduction of “naked” DNA**
- **viruses**

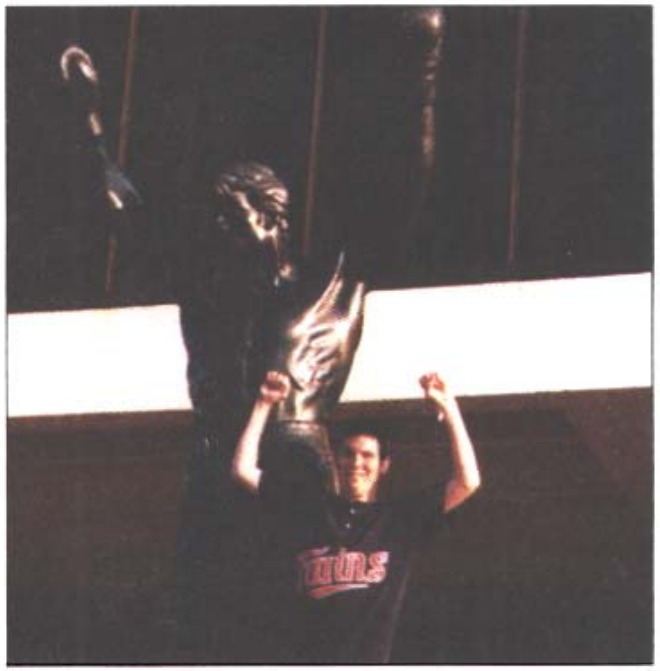

retrovirus
human
target cell
RNA
Reverse
transcription
DNA
random integration into host DNA
Nucleus
therapeutic gene product

adenovirus



no/directed integration into host DNA

With many unanswered questions, how should we use gene therapies and how much are we willing to risk?



Jesse Gelsinger