Section 3 of X143: Modern Genetics

1. Developmental Genetics
2. Genomics & Bioinformatics
3. Population Genetics
4. Quantitative Genetics
5. Evolutionary Genetics

The question: Can we use the basic principles of genetics to begin to understand the amazing diversity of phenotypes in organismal life on the planet?

Traditionally Separate Subjects

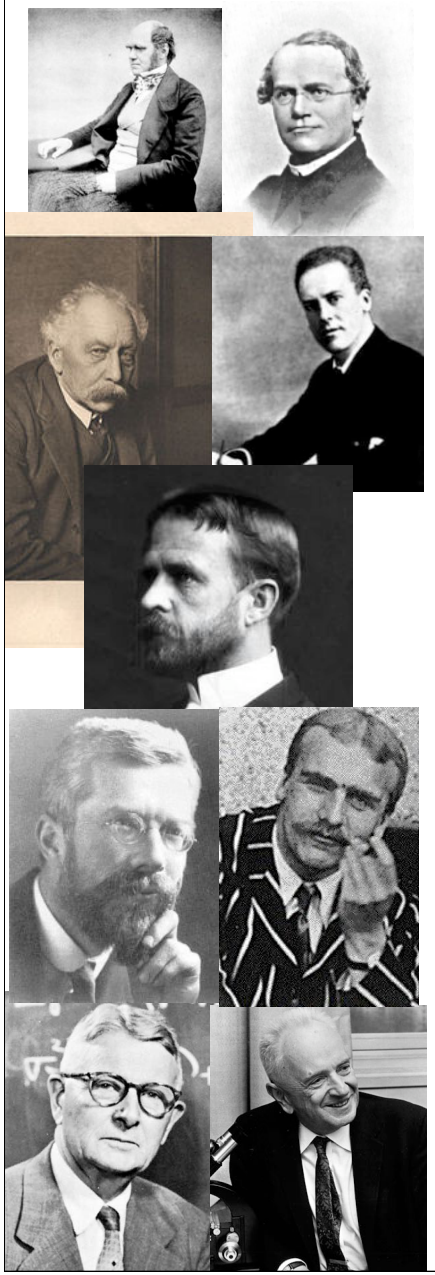
Systematics (species classification & relationships)

Biometry (quantitative descriptions of phenotypes)

Experimental Biology

Mendelian/Population Genetics

A little history leading to The Modern Synthesis (Neo-Darwinism)



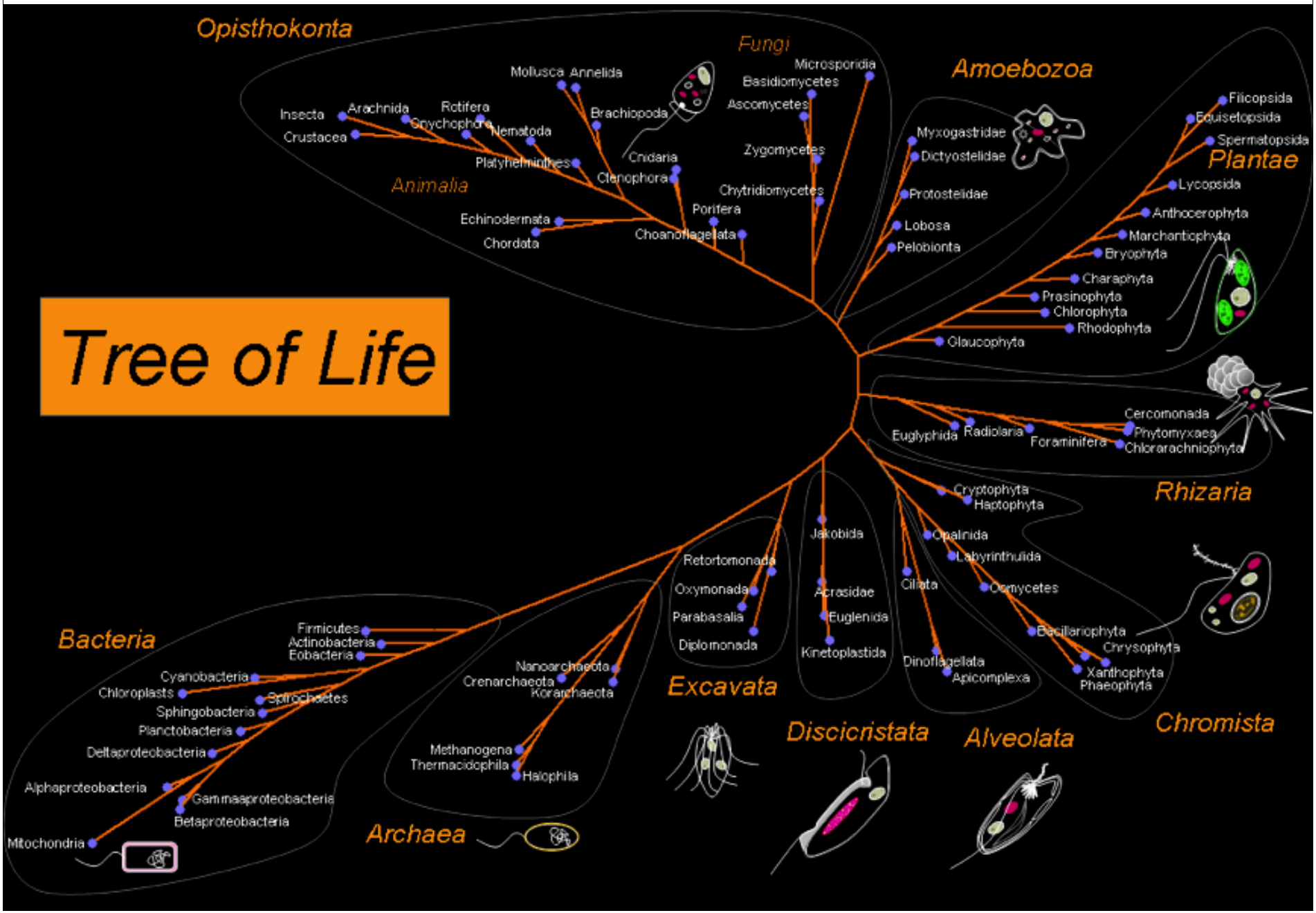
1859 - Charles Darwin's *On the Origin of Species*
1866 - Gregor Mendel's *Experiments in Plant Hybridization*
1900 - Mendel "rediscovered" by William Bateson but generality doubted by biometricians such as Karl Pearson because of continuous variation in most traits
1915 - T. H. Morgan's *The Mechanism of Mendelian Inheritance* verifies Mendel's work and solidifies chromosomal heredity
1918 - R. A. Fisher breaks controversy by developing theory of complex Mendelian inheritance leading to continuous trait variation
1924 - J. B. S. Haldane & Sewall Wright advance Fisher's theories and establish fundamentals of population genetics
1937 - Theodosius Dobzhansky's *Genetics and The Origin of Species* combines Darwin's natural selection, Mendel's genetic inheritance, Morgan's chromosomal basis of genetic variation and population genetic theory into a single unified field of modern genetics

The Modern Synthesis:

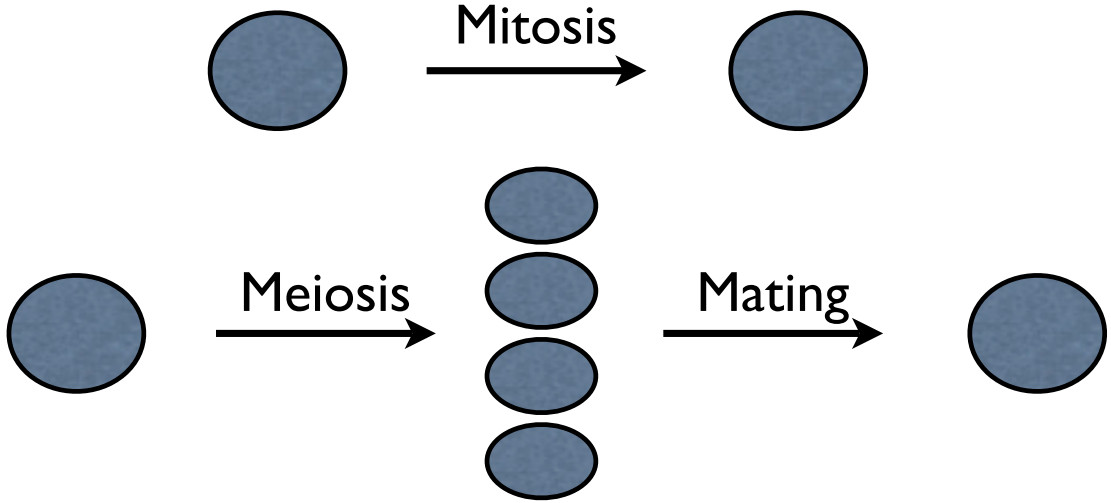
- Mid-20th century unification of traditionally distinct fields of Systematics, Biometry, Experimental Biology and Genetics (Development).
- Establishes mutation and recombination of chromosomes as the sources of genetic variation
- Establishes that discrete Mendelian genetics is the basis of heredity
- Establishes that Darwinian natural selection can act on genetic variation in populations to lead to adaptation and speciation

The Genetic Control of Development

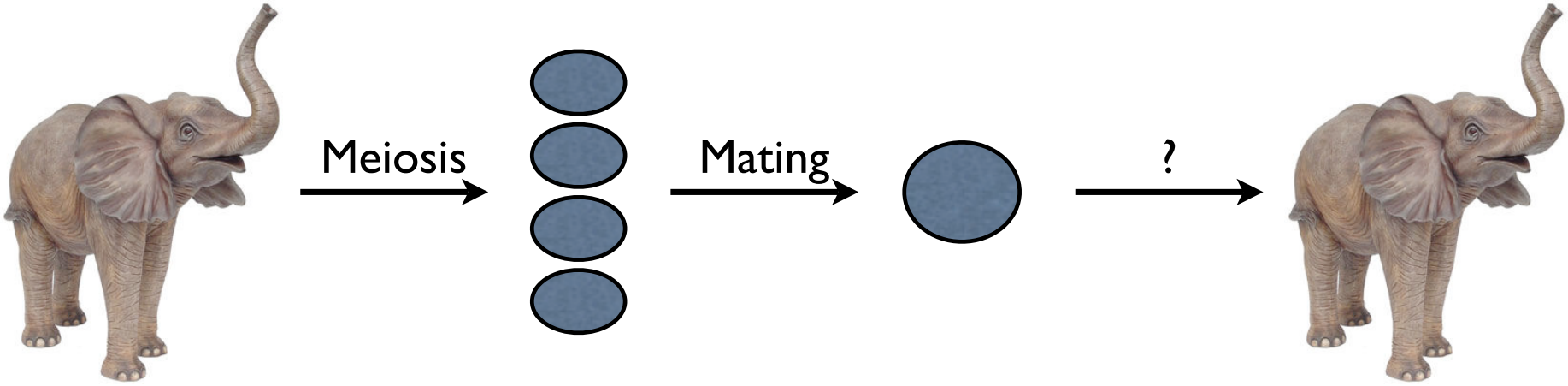
Multi-cellularity appears to have evolved many times

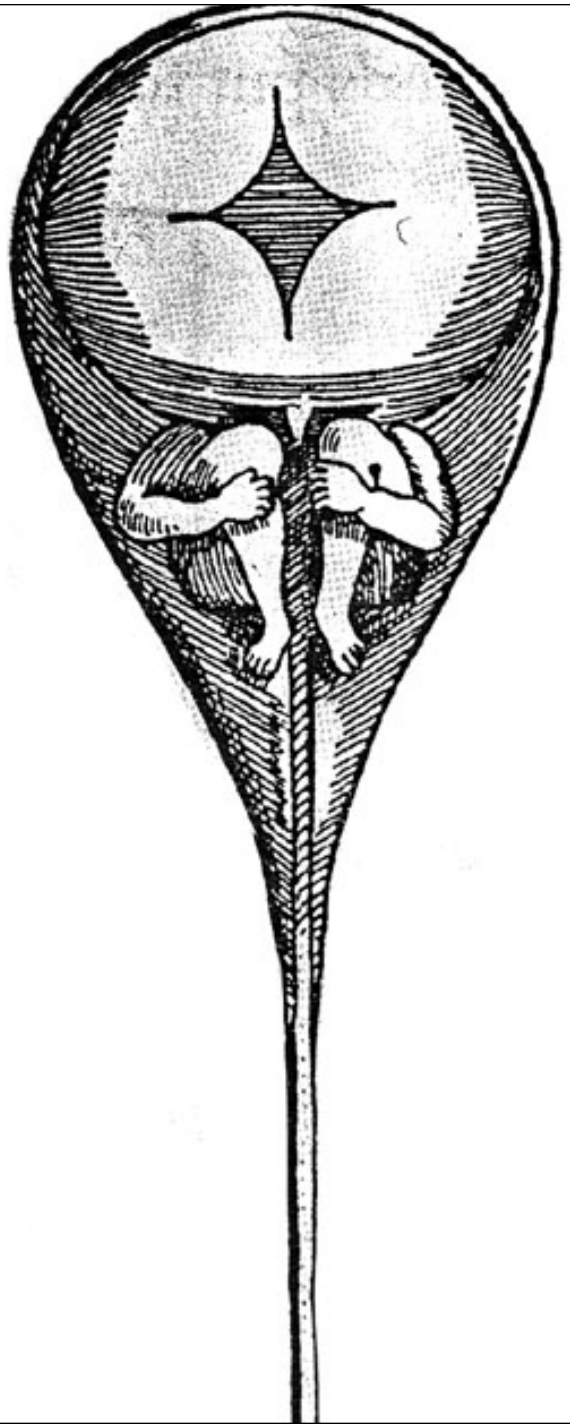


Unicellular reproduction:



Multicellular reproduction:

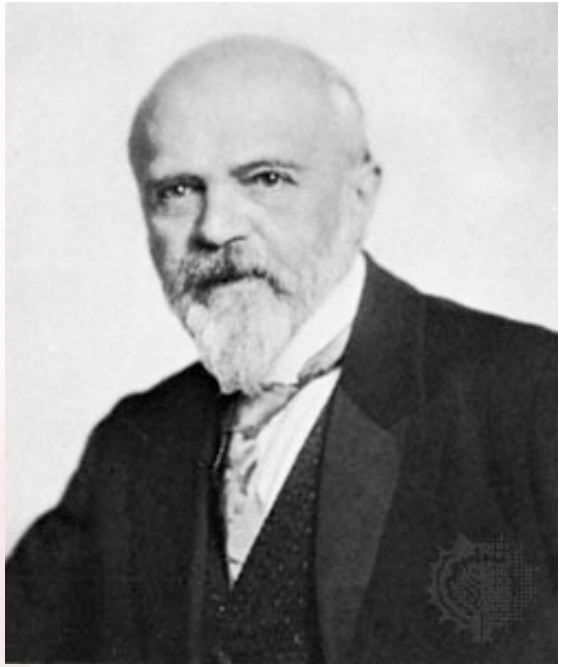


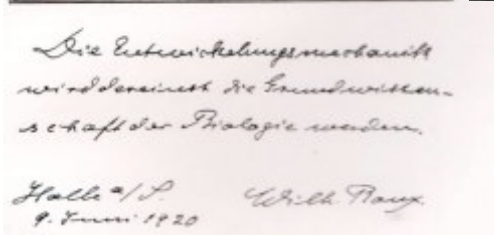


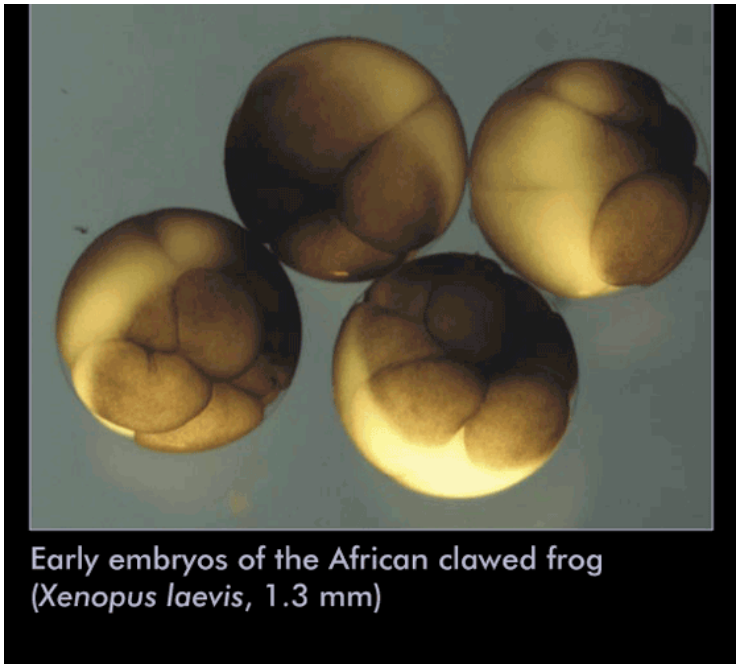
Niklaas Hartsoeker's famous drawing of a "homunculus" inside of a sperm from 1664.

Study of development began with simple manipulation of embryos in the late 19th century

Wilheml Roux Hans Driesch

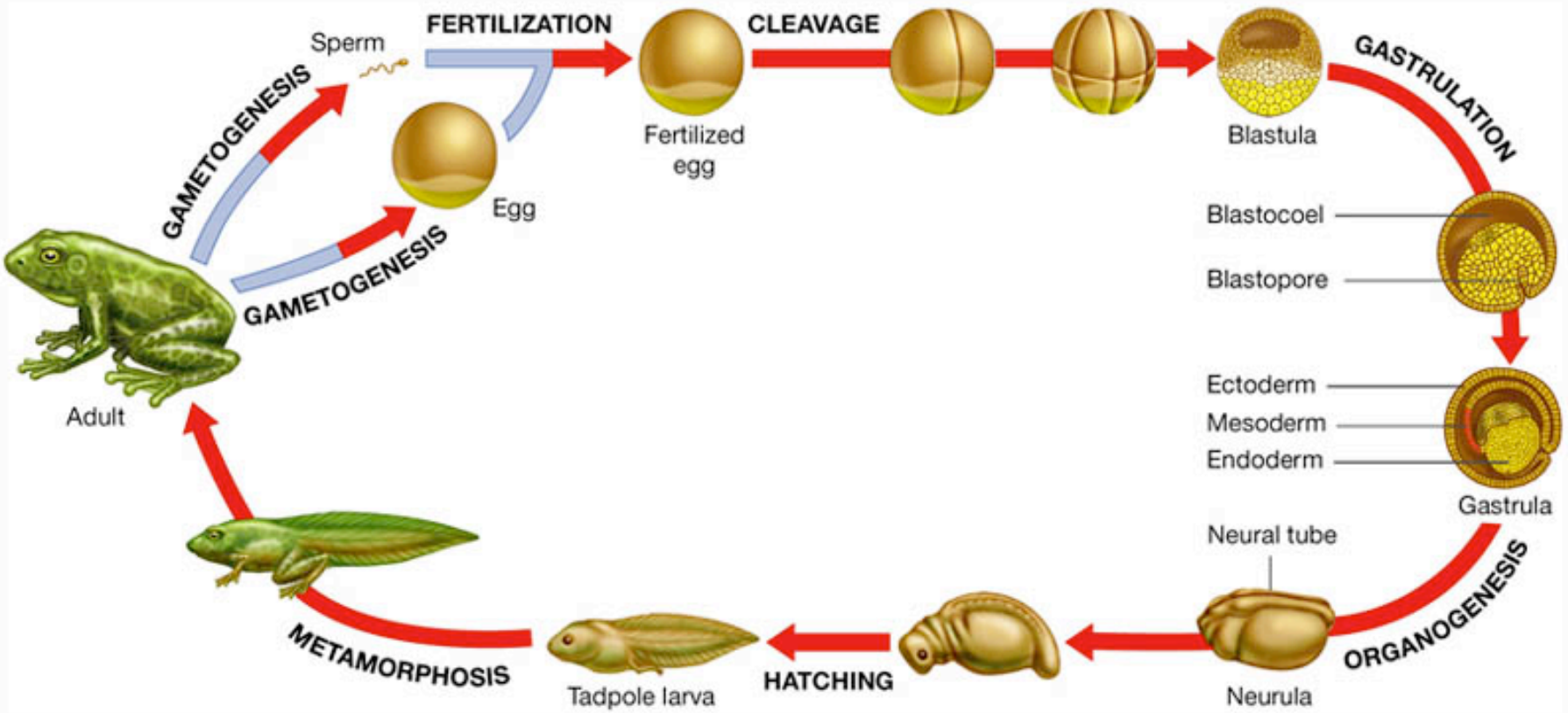




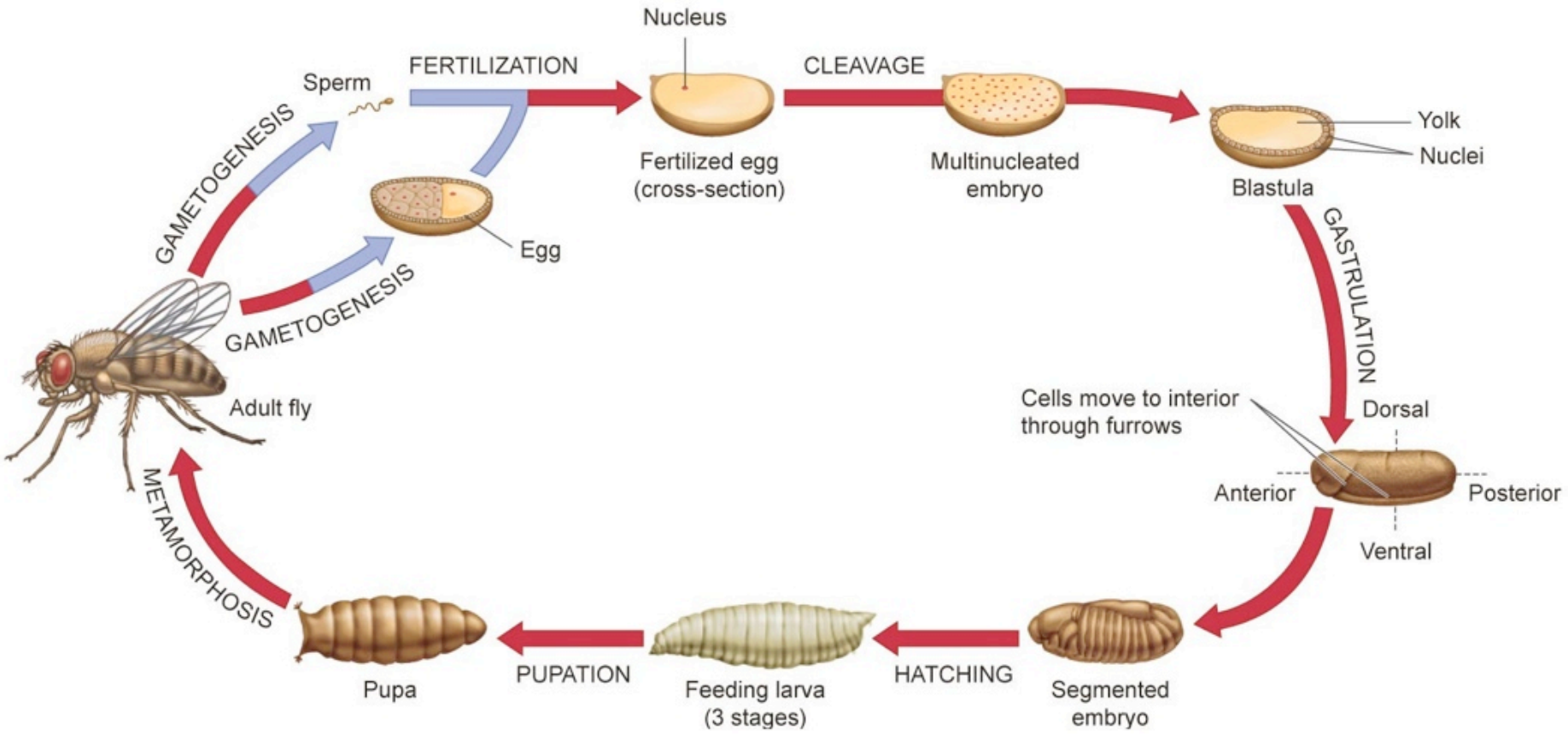


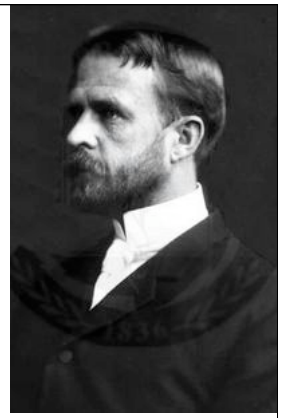
Early embryos of the African clawed frog
(*Xenopus laevis*, 1.3 mm)

Frog Development



Drosophila Development



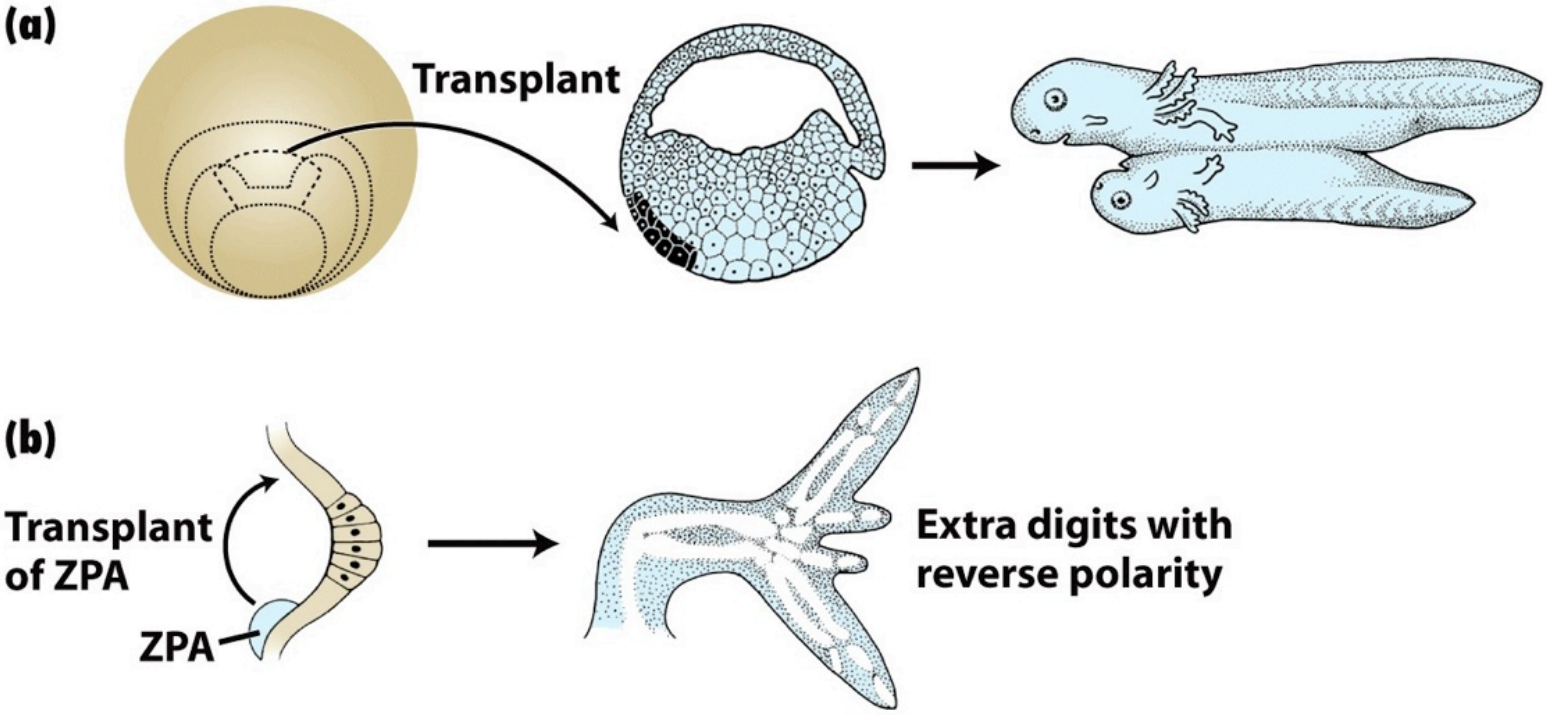


"A transparent egg as it develops is one of the most fascinating objects in the world of living beings. The continuous change in form that takes place from hour to hour puzzles us by its very simplicity. The geometric patterns that present themselves at every turn invite mathematical analysis. This pageant makes an irresistible appeal to the emotional and artistic sides of our nature."

"...if the mystery that surrounds embryology is ever to come within our comprehension, we must ... have recourse to other means than description of the passing show."

-T. H. Morgan

Early study of development was descriptive and lacked mechanistic understanding



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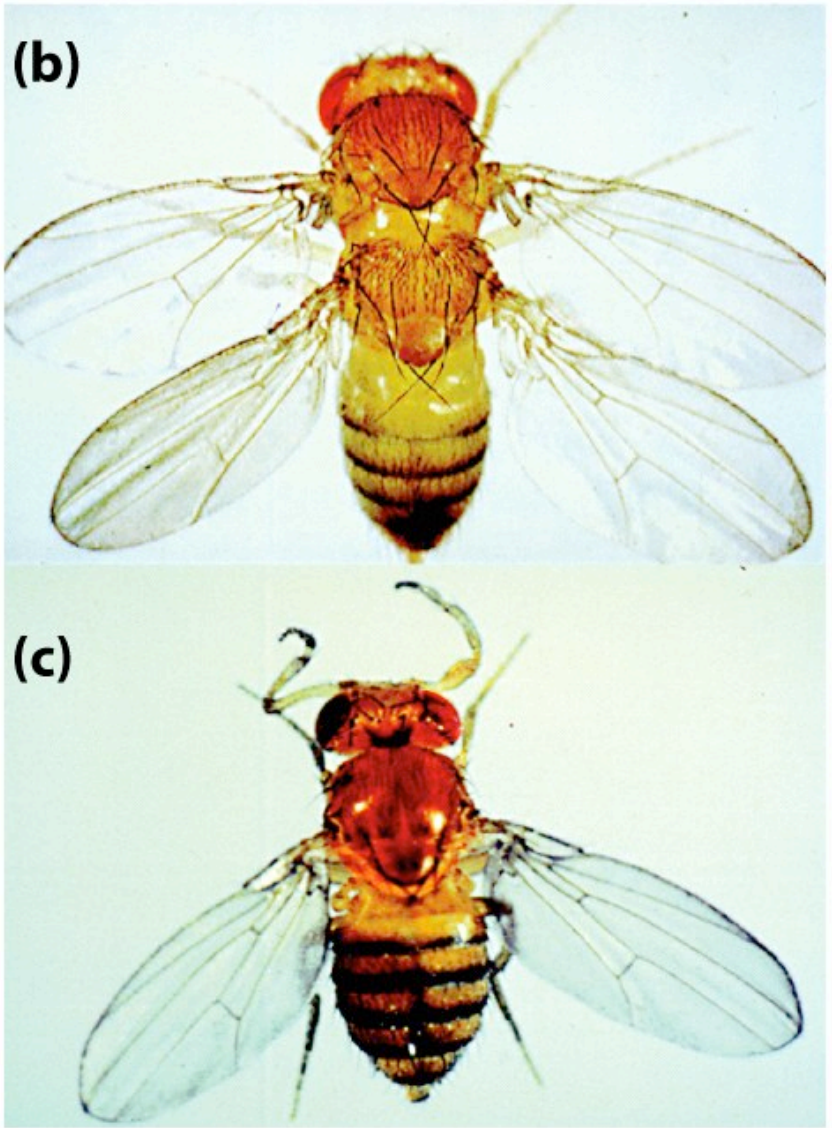
1. Transplantation assays reveal some cells organize their surrounding tissue while other cannot
2. 'Organizers' postulated to produce diffusible 'morphogens' that induce specific cell fates, however, biochemical isolation of these molecules proved impossible

Homeotic mutants in Drosophila: Identity of one body structure has been changed into another



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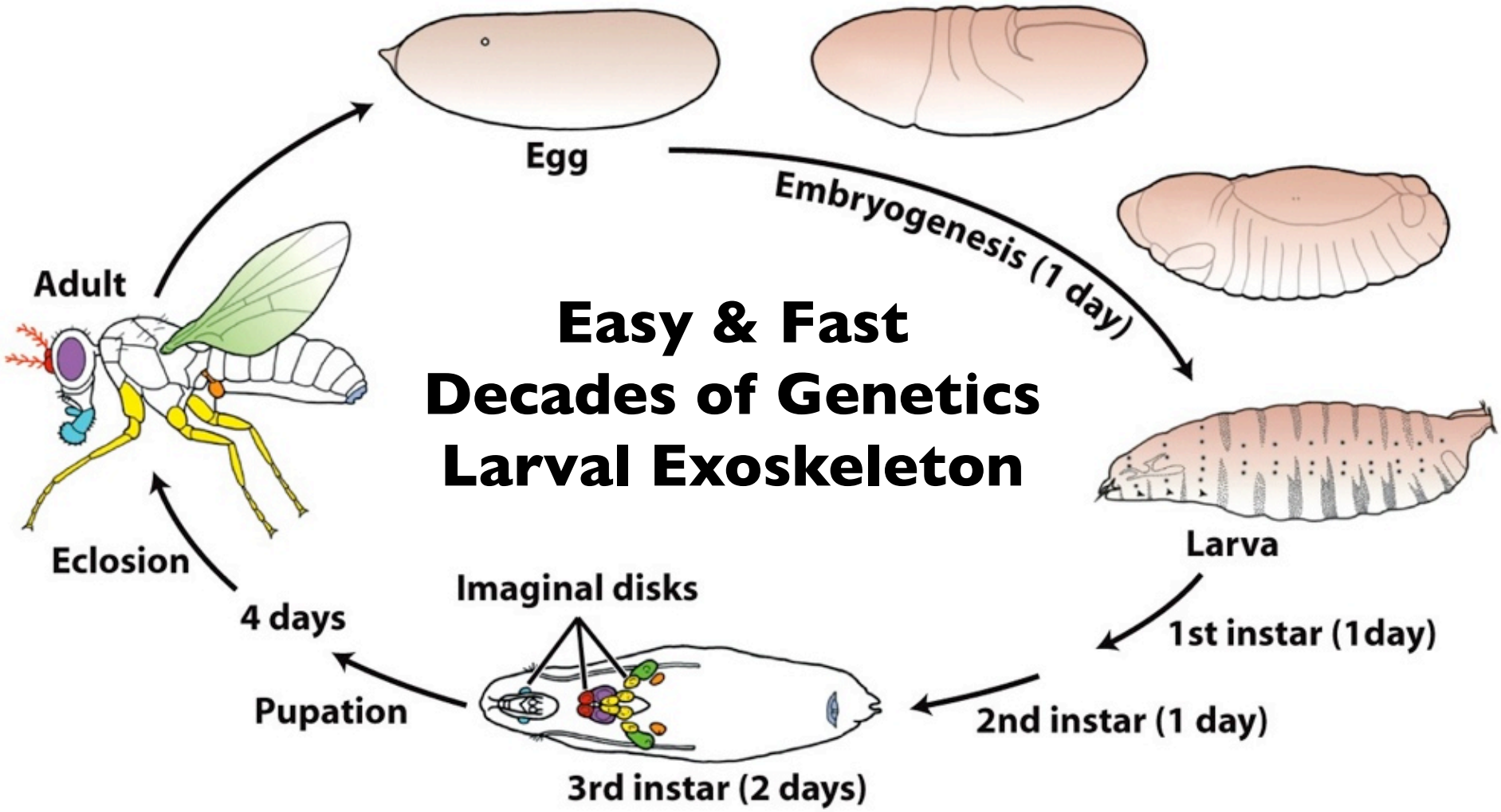
Advantages of the genetic approach to development over physical manipulation and biochemistry:

1. No prior knowledge needed about number or types of molecules
2. All genes can be mutated and therefor studied regardless of the number of molecules they produce
3. Genetics can discover processes for which no good manipulation or biochemical assay exists

Basic goals of a developmental geneticist:

1. Which genes are involved?
2. Where and when are these genes expressed?
3. How is their expression controlled?
4. What are their molecular roles?

Key advantages of the Drosophila system



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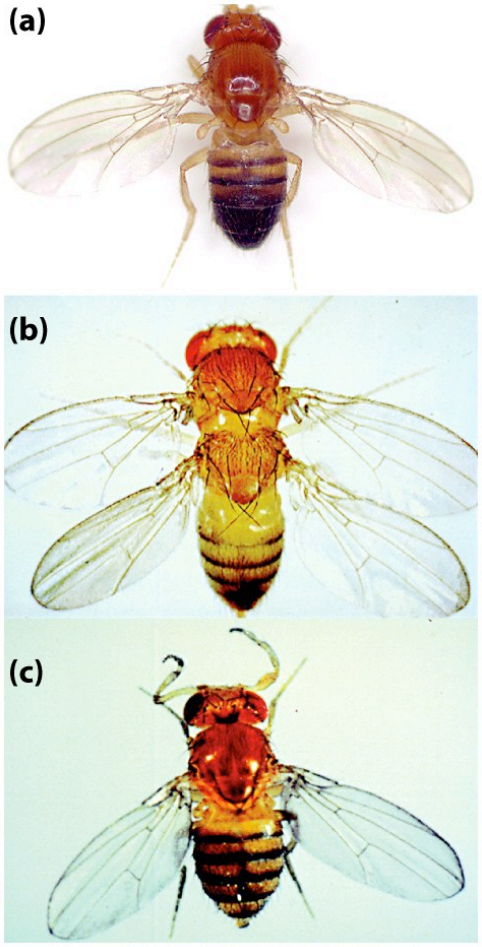
How can the genes involved in development be identified?

1. Study spontaneous mutants (i.e. Antennapedia)
2. Study mutations induced at random by treatment of mutagens (chemicals or radiation)

What are the advantages and disadvantages to these two methods?

Homeotic genes: the remarkable mutants



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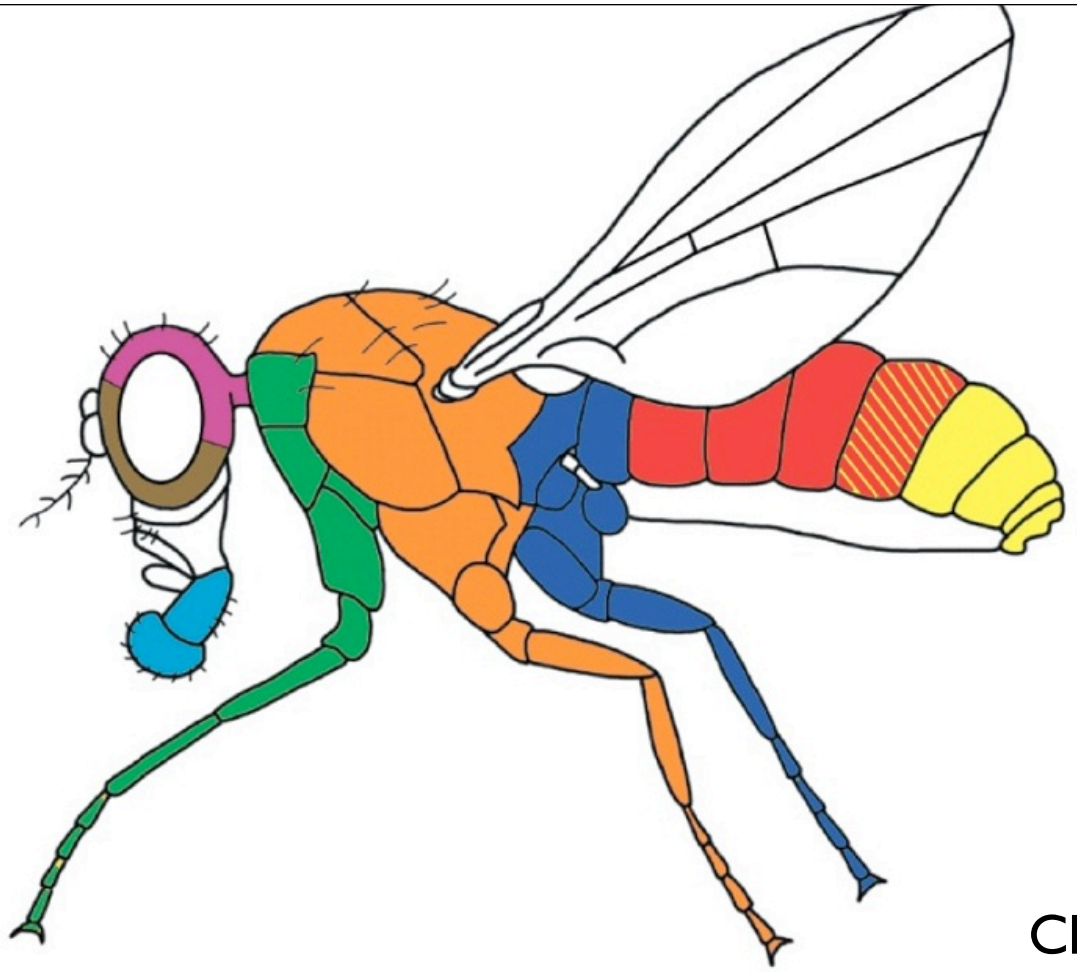
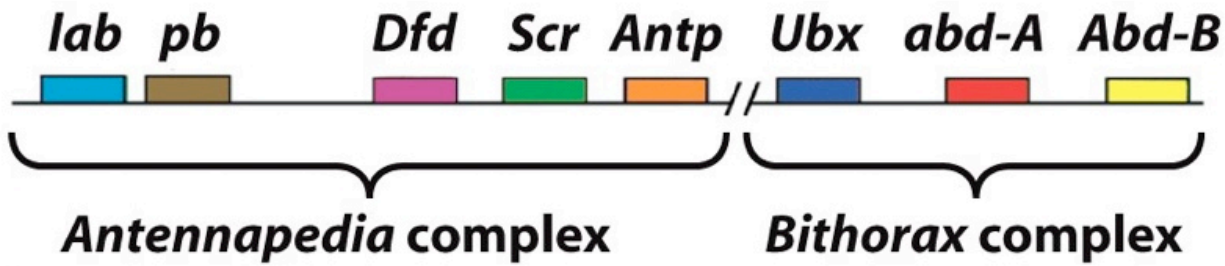
- very dramatic for single gene mutants
- great likeness of transformed structure to other body part
- transform **serially reiterated structures** (common feature of animal form)
- genetic screens have identified 8 loci referred to as the **Hox genes**
- most adult transforming mutants are dominant and homozygous nulls are lethal



Chromosome 3



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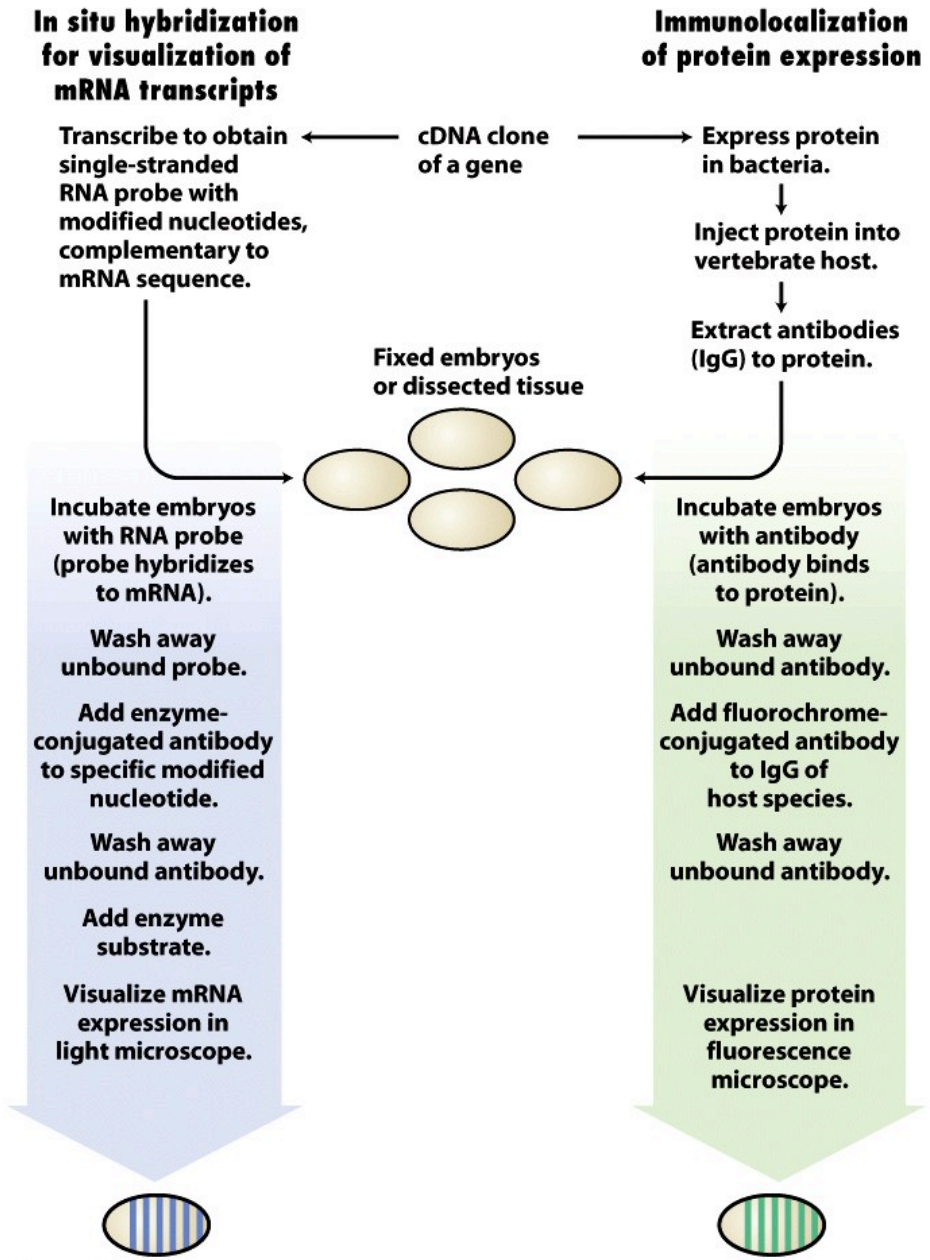
Techniques for visualizing expression of cloned genes:

1. In situ for mRNA
2. Immunohistochemistry for protein



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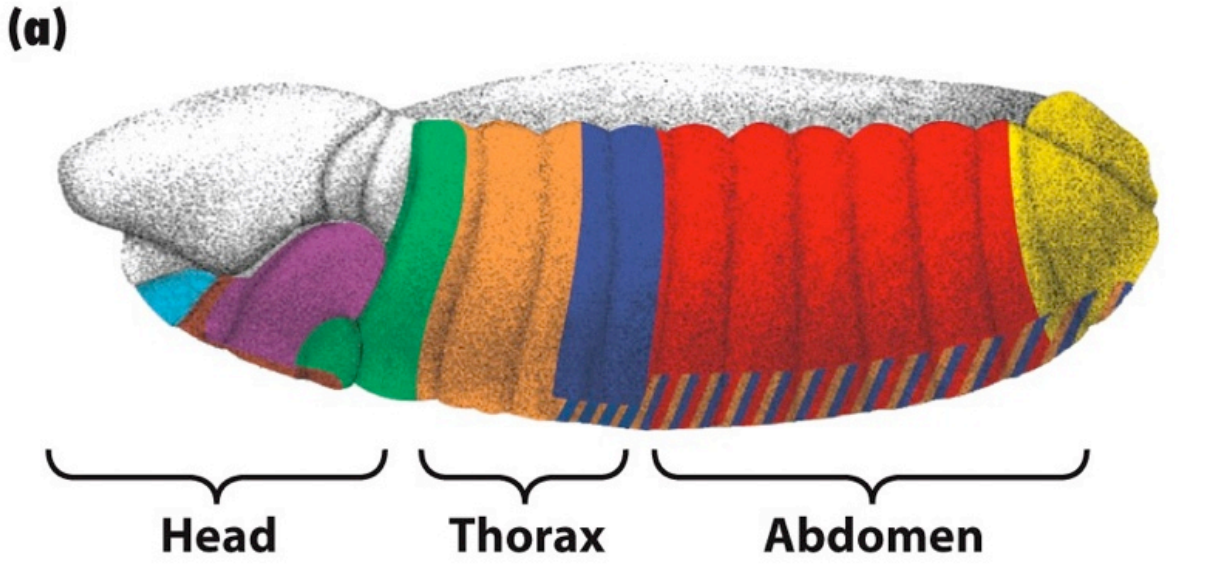

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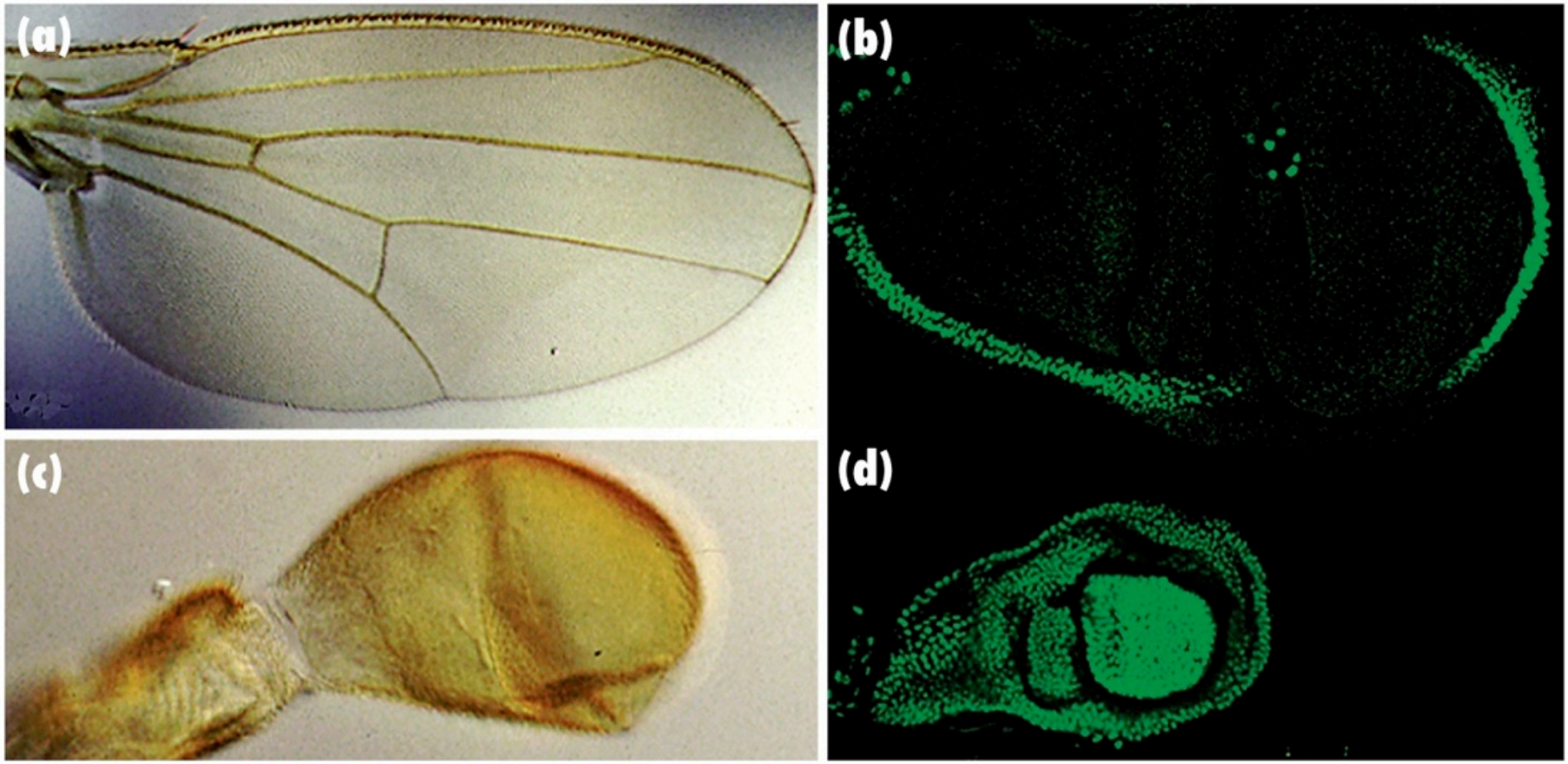
Hox genes are expressed in structures affected by mutants for each gene (Ubx)



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Basic goals of a developmental geneticist:

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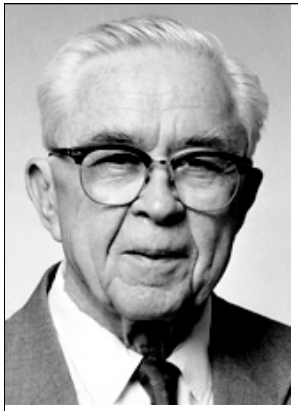

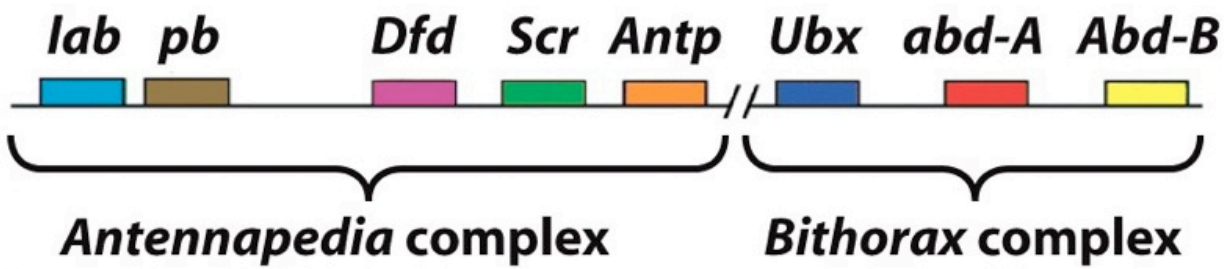

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Ed B. Lewis (Nobel 1995)

Hypothesis: Because the Hox genes are found in clusters, perhaps they arose from tandem duplication of a single gene and therefor perhaps have the same molecular function.

Experiment: Try to hybridize Hox genes to each other.

Result: All cross-hybridized and this could be mapped to a 180bp region in each gene, dubbed the "homeobox".

Homeobox is a helix-turn-helix DNA binding domain called the homeodomain

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- Structure of homeodomain revealed helix-turn-helix motif
- Same motif found in the Lac repressor and alpha2 and a1 from yeast mating type loci
- Suggested Hox are DNA binding proteins that regulate gene expression within developing segments
- Subsequently tested and verified

Hox genes found broadly across animals

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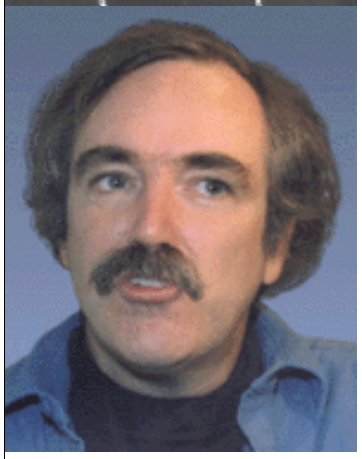
Why were Hox proteins highly conserved over 500 million years of evolution?



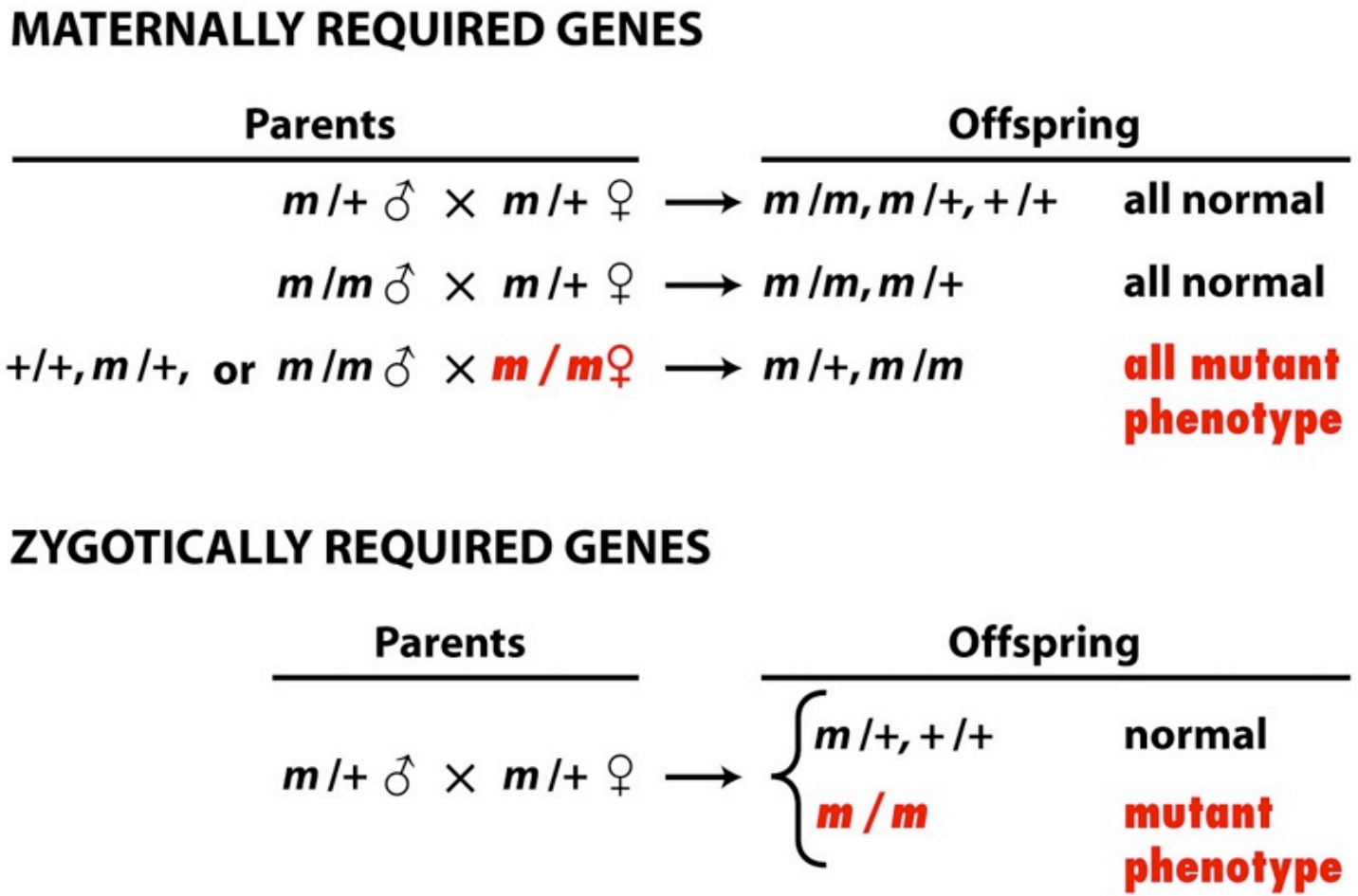
Christine Nusslein-Volhard &
Eric Wieschaus
(Nobel 1995 w/ Ed Lewis)

How can we find genes that set up the segments in the embryo?

- Most research had focused on mutants with adult phenotypes
- Probably lethal during development in homozygous mutants

How would you design such a screen?

Major advancements: saturated each chromosome for mutations, screened embryos not adults and carefully examined embryonic phenotypes (not just viability)



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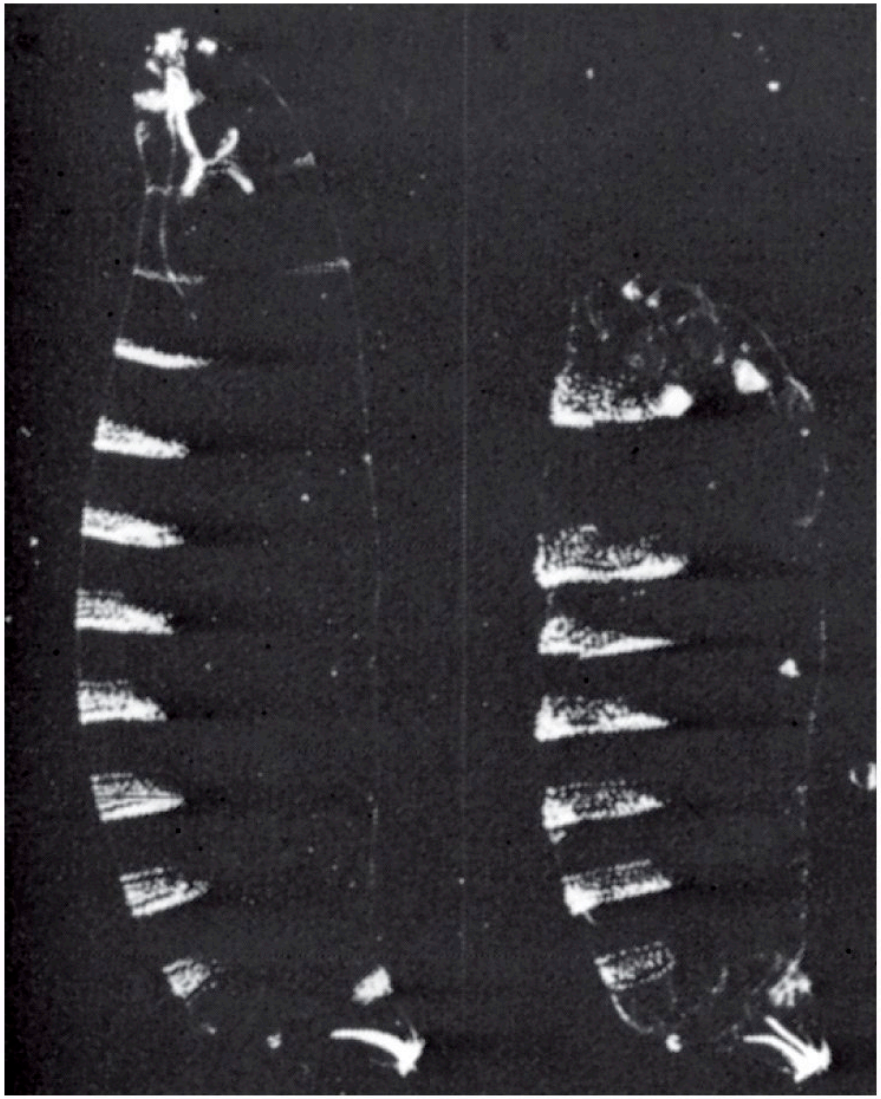
Wildtype *Bicoid* mutant



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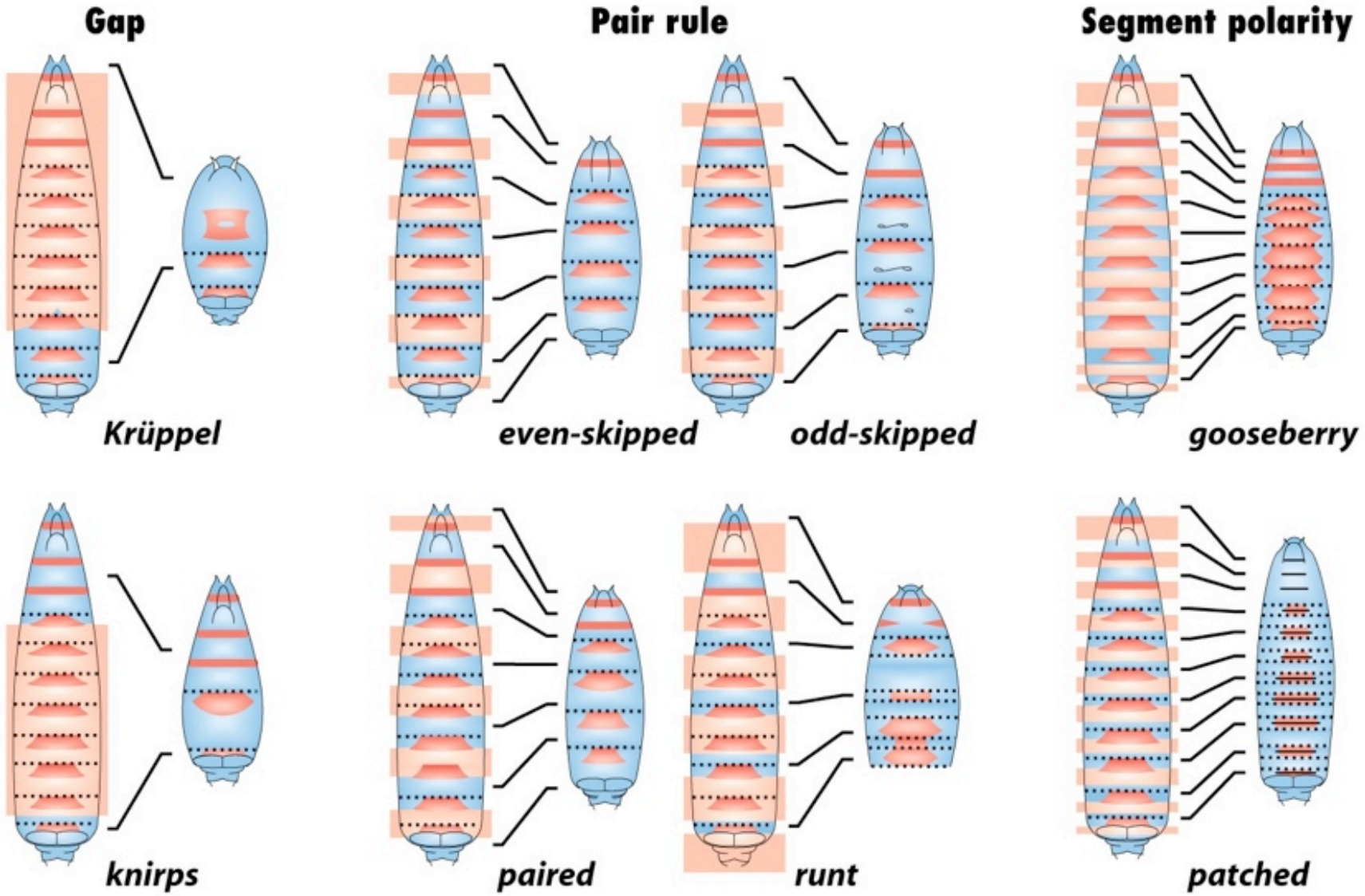
Example of a maternal-effect mutant called Bicoid (bcd):
- exoskeleton reveals the phenotype
- head and thoracic structures are missing in mutant (right)

Genes affecting anteroposterior body axis formation



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Basic goals of a developmental geneticist:

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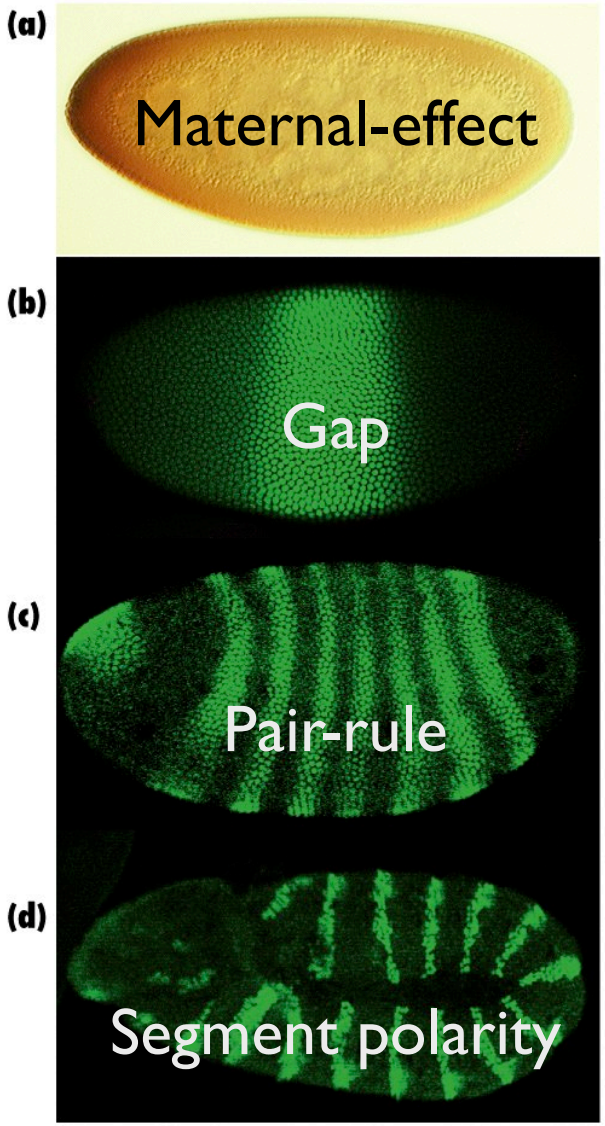
Expression patterns of AP genes suggest a network



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1. Expression domains correspond to locations of mutant phenotypes
2. Expression refines through time implying each stage regulates the next stage
3. Mutants affect expression of some genes expressed later

AP genes predominantly transcription factors and signaling supporting network hypothesis

Table 12-1 Examples of *Drosophila* A–P Axis Genes That Contribute to Pattern Formation

Gene symbol	Gene name	Protein function	Role(s) in early development
hb-z	*hunchback-zygotic*	Transcription factor—zinc-finger protein	Gap gene
Kr	*Krüppel*	Transcription factor—zinc-finger protein	Gap gene
kni	*knirps*	Transcription factor—steroid receptor-type protein	Gap gene
eve	*even-skipped*	Transcription factor—homeodomain protein	Pair-rule gene
ftz	*fushi tarazu*	Transcription factor—homeodomain protein	Pair-rule gene
opa	*odd-paired*	Transcription factor—zinc-finger protein	Pair-rule gene
prd	*paired*	Transcription factor—PHOX protein	Pair-rule gene
en	*engrailed*	Transcription factor—homeodomain protein	Segment-polarity gene
ci	*cubitus-interruptus*	Transcription factor—zinc-finger protein	Segment-polarity gene
wg	*wingless*	Signaling WG protein	Segment-polarity gene
hh	*hedgehog*	Signaling HH protein	Segment-polarity gene
fu	*fused*	Cytoplasmic serine/threonine kinase	Segment-polarity gene
ptc	*patched*	Transmembrane protein	Segment-polarity gene
arm	*armadillo*	Cell-to-cell junction protein	Segment-polarity gene
lab	*labial*	Transcription factor—homeodomain protein	Segment-identity gene
Dfd	*Deformed*	Transcription factor—homeodomain protein	Segment-identity gene
Antp	*Antennapedia*	Transcription factor—homeodomain protein	Segment-identity gene
Ubx	*Ultrabithorax*	Transcription factor—homeodomain protein	Segment-identity gene

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Questions to ponder for next time:

Do the AP genes regulate each other?

If so, how can simple expression patterns (like the gap genes) lead to more complex expression patterns (like segment polarity genes)?

What are the mechanisms involved?