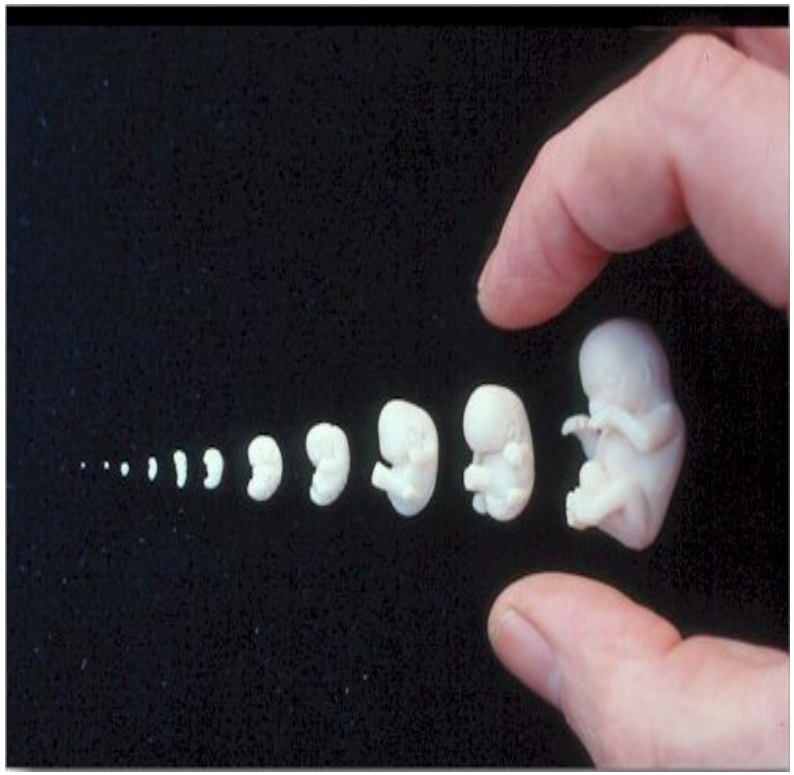
4. GROWTH, REGENERATION, AGEING AND EVOLUTION

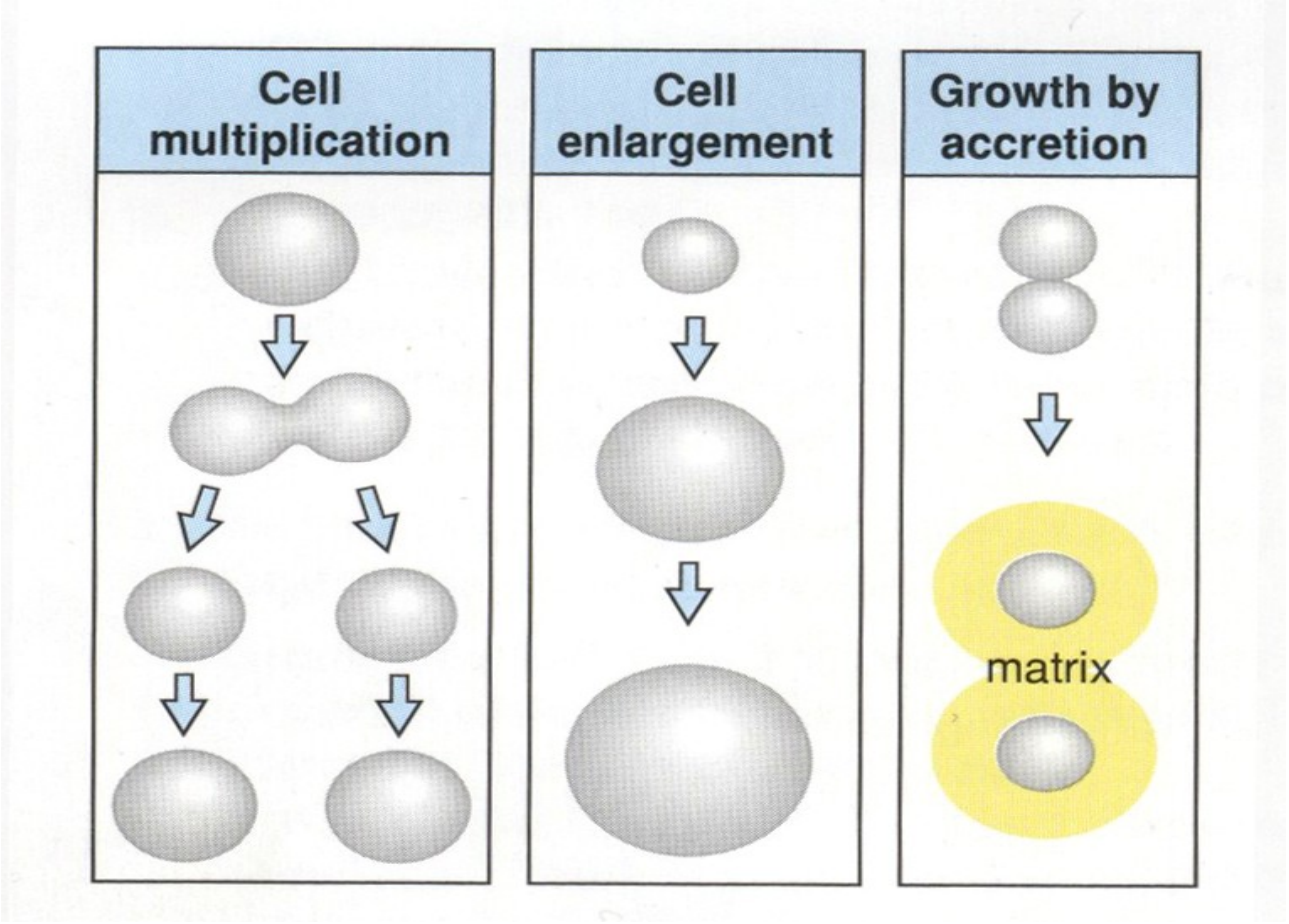
GROWTH: the least well understood aspect of development



x 10^9 =

FORM/PATTERN **vs.** **GROWT/PROPORTION**

Intracellular mechanisms that drive cell growth are well understood but overall growth control remains largely mysterious.



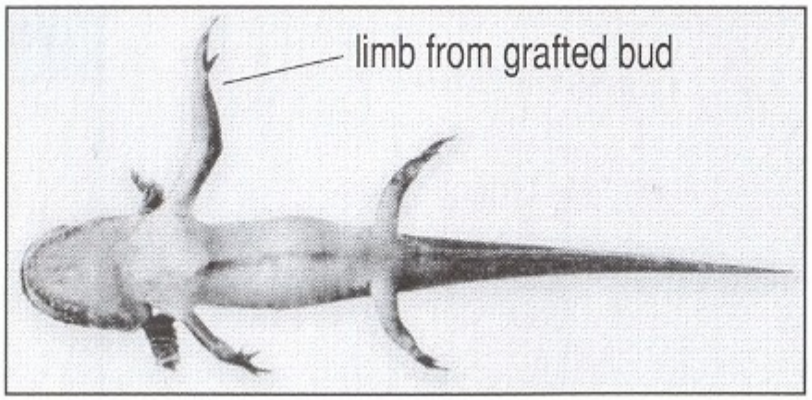
MYSTERIES: regulation of final size

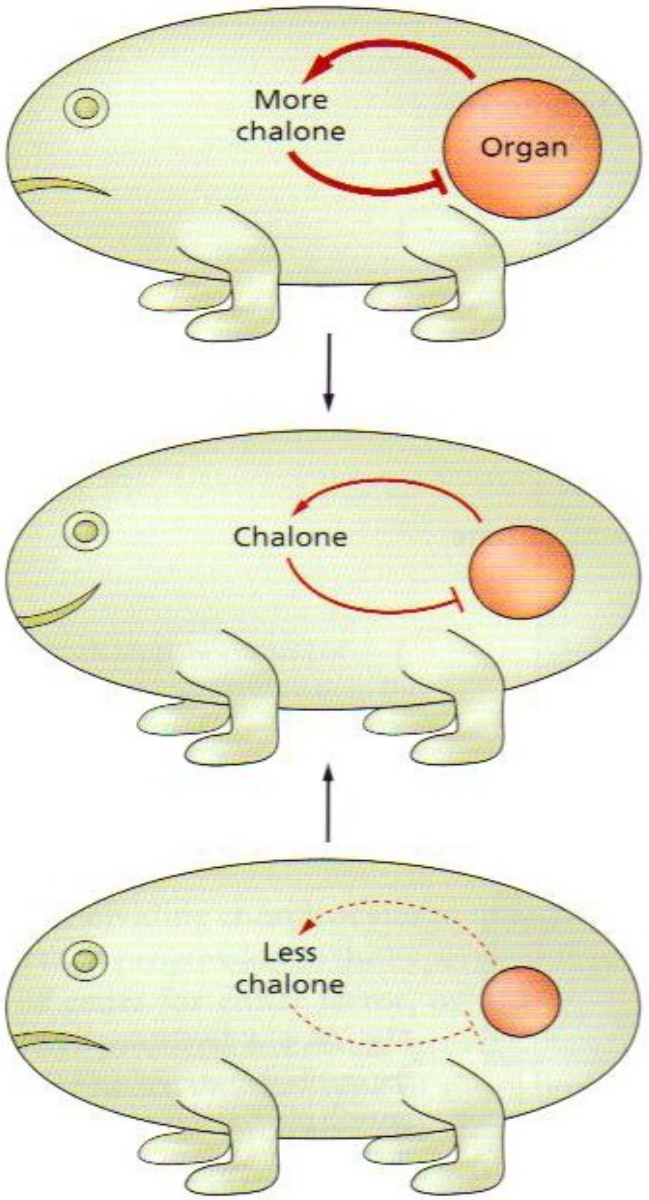
Why some stop growing while others grow indefinitely?

Is final animal size limited by nutrient supply that is restricted by the amount of terminal capillaries which can not grow as fast as the volume of the 3D object?

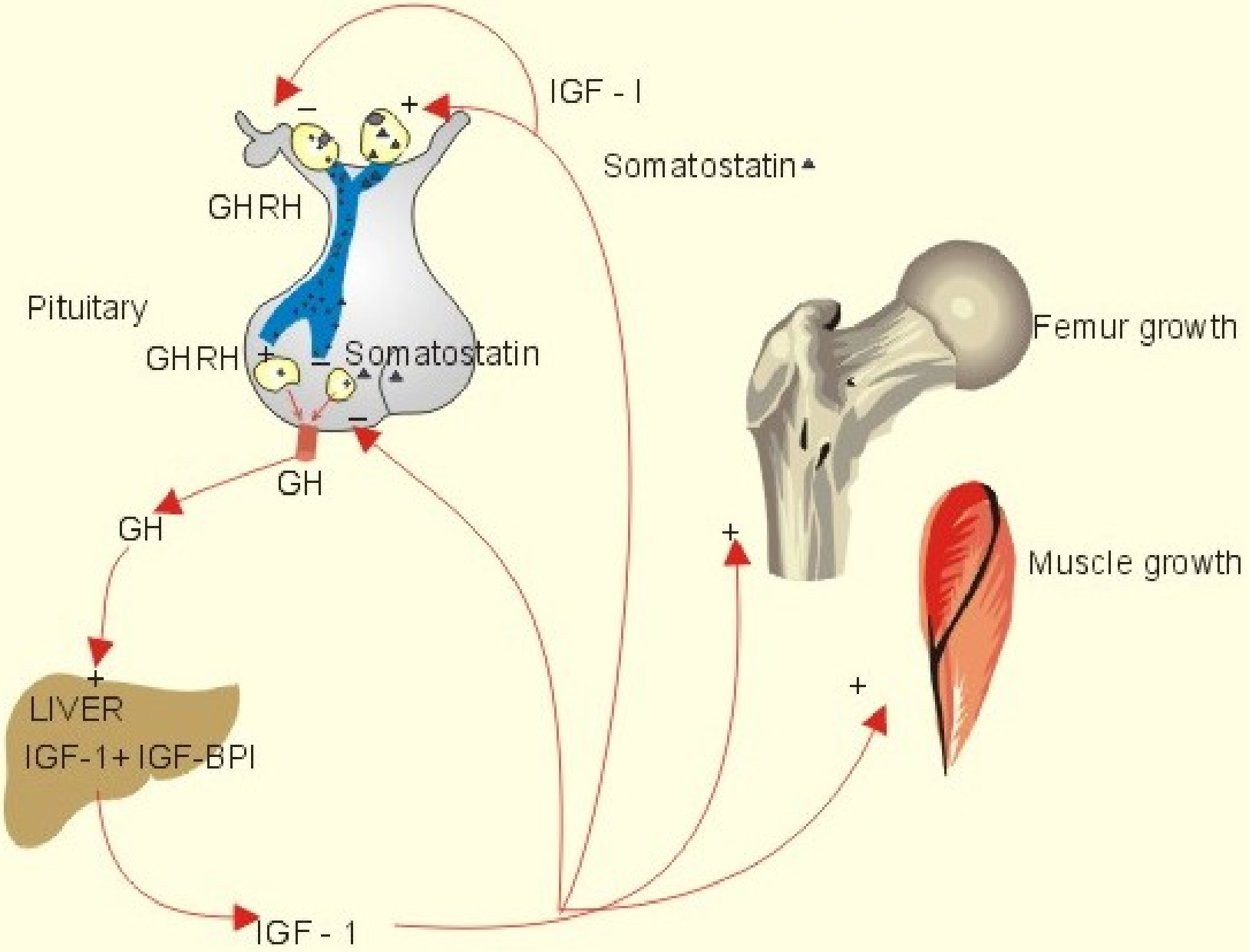
MORE MYSTERIES: control of relative proportions

Why there are usually no overgrown parts?



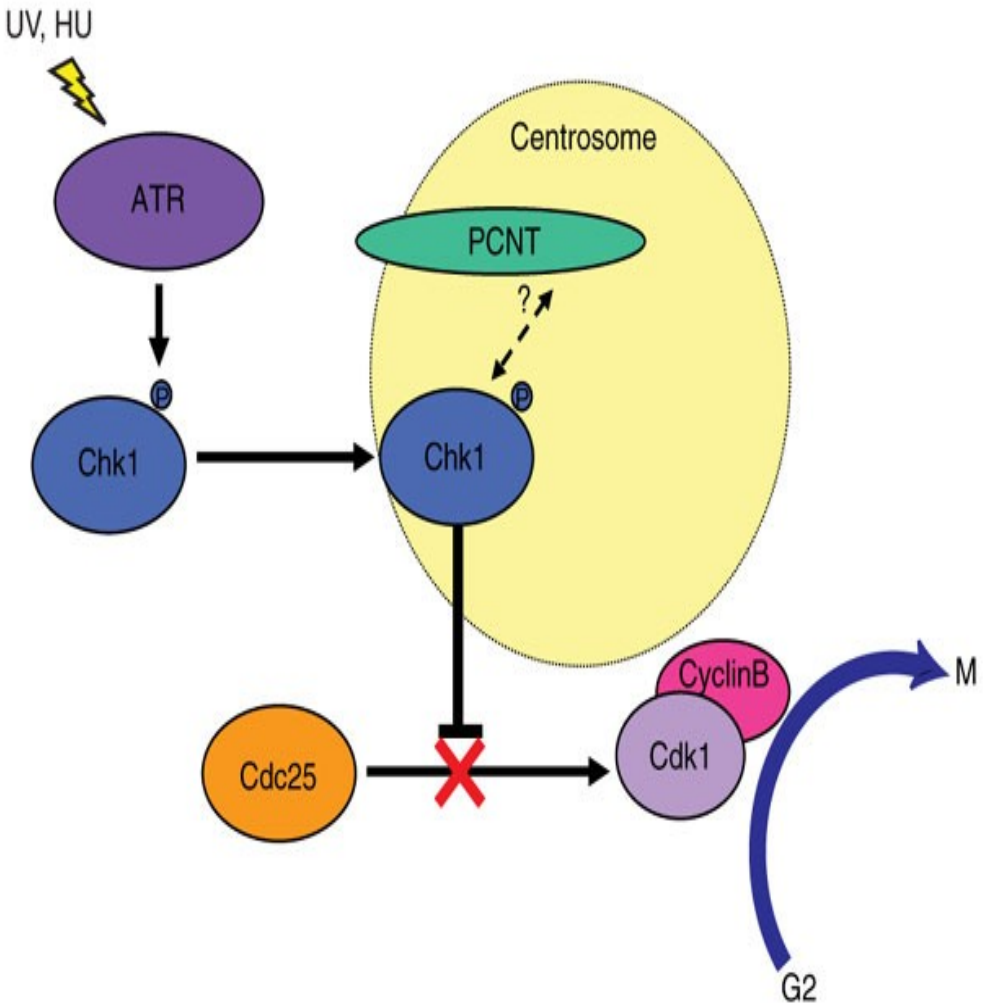


Hypothalamus And Growth

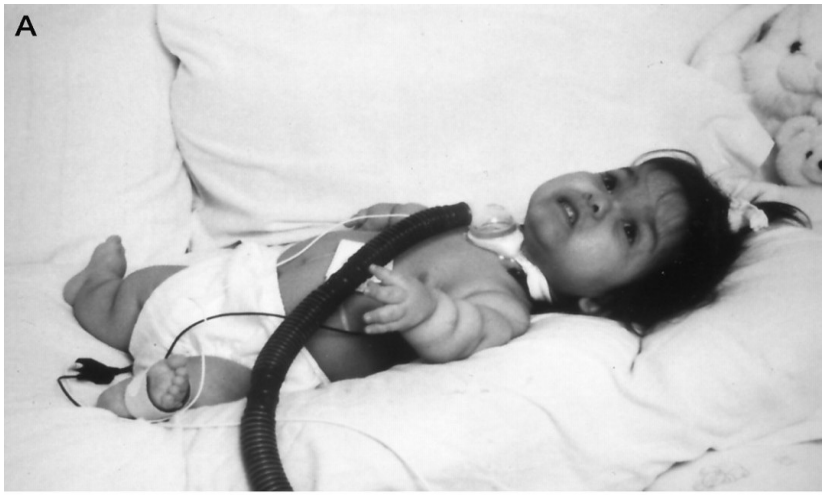


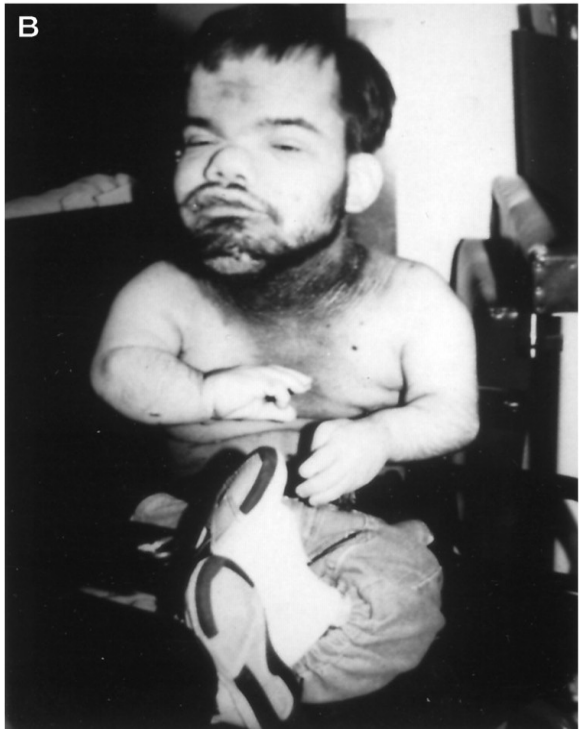
Soft tissues grow in proportion to the skeleton

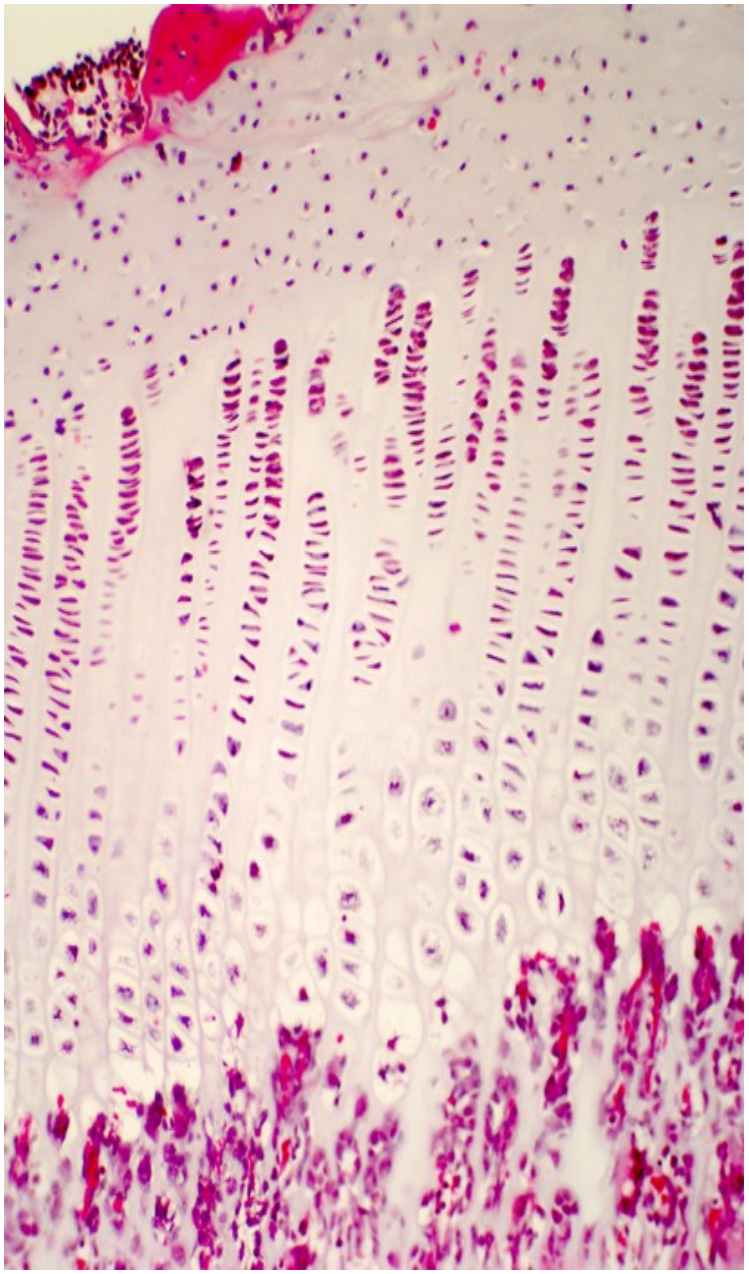
Pericentrin

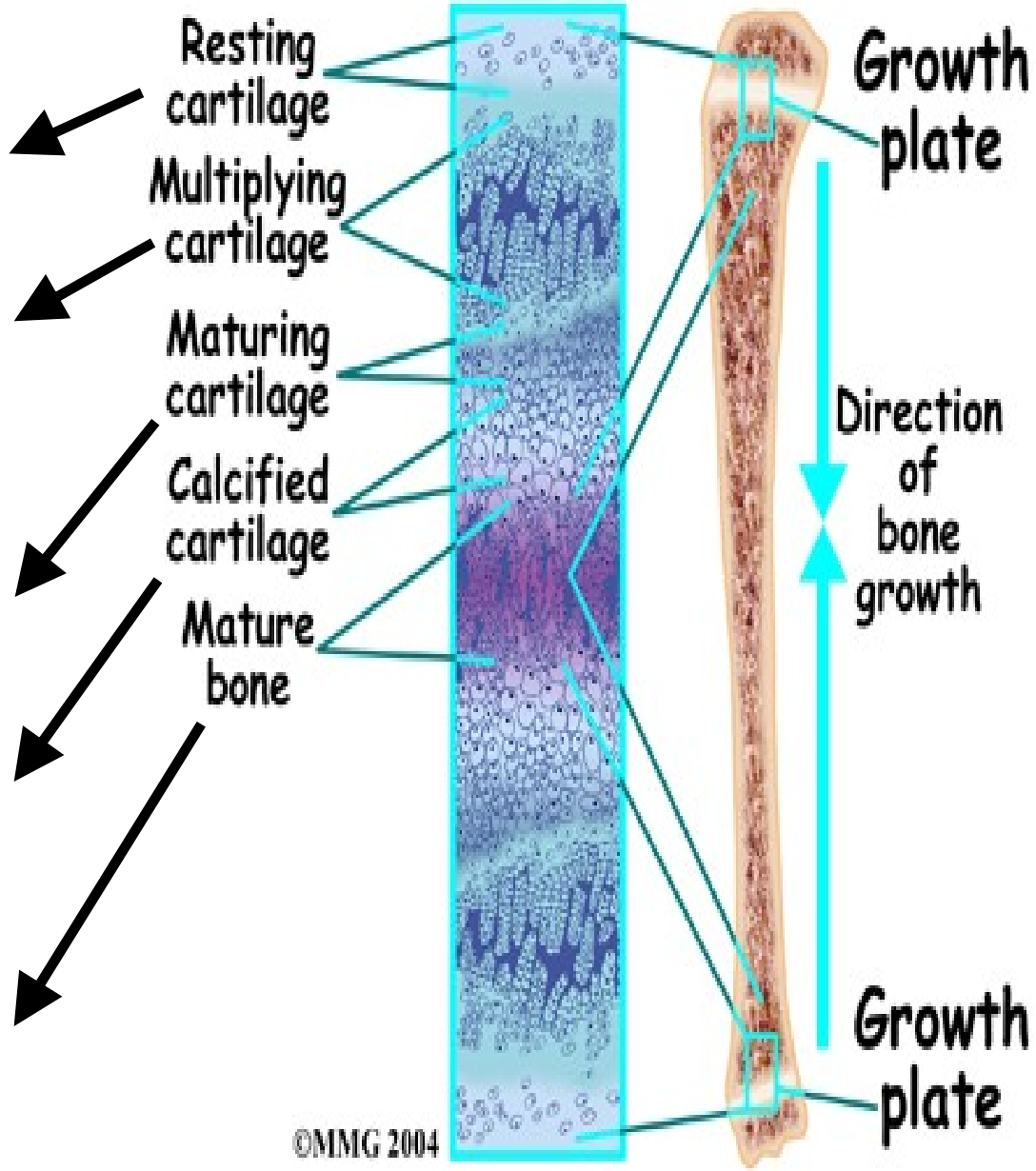


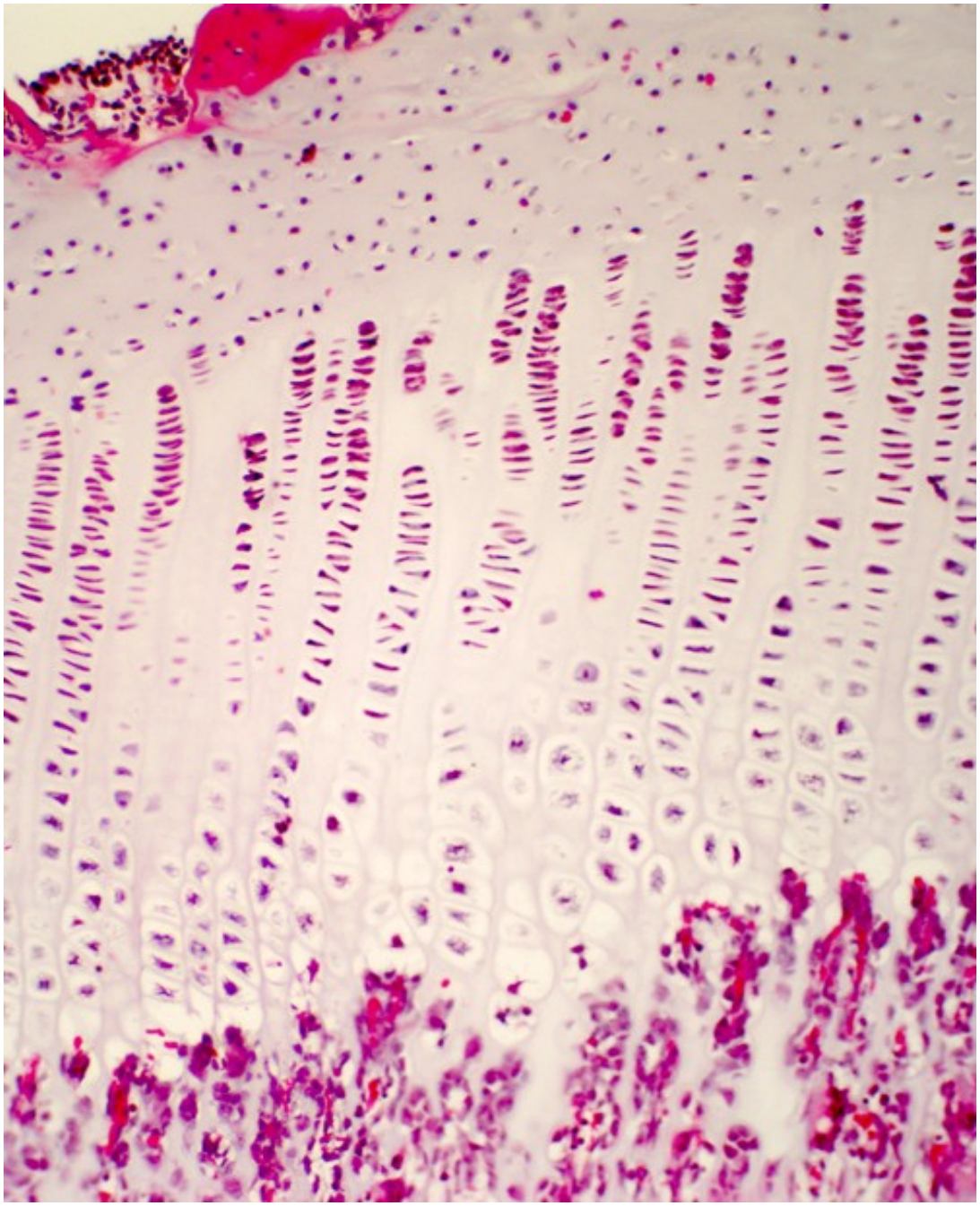
SADDAN








Resting cartilage
Multiplying cartilage
Maturing cartilage
Calcified cartilage
Mature bone
Growth plate
Direction of bone growth
Growth plate
©MMG 2004

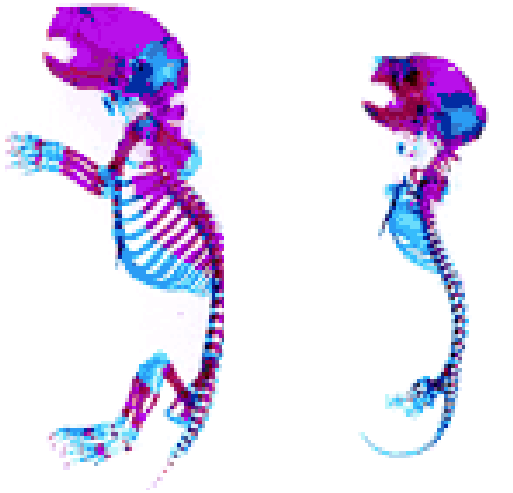


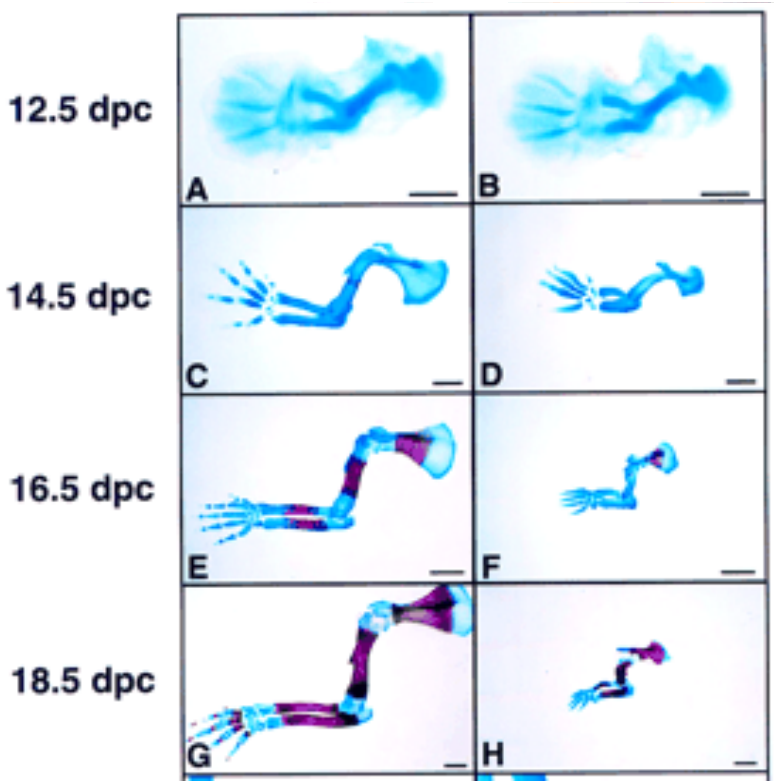
TOTAL GROWTH

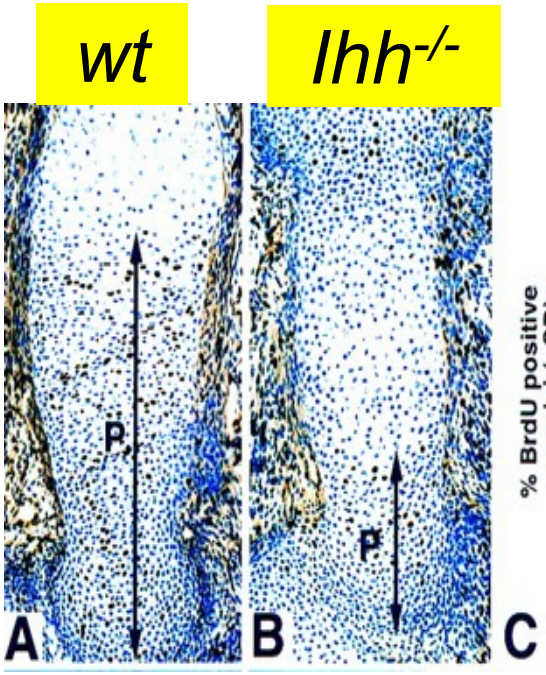
50% cell proliferation

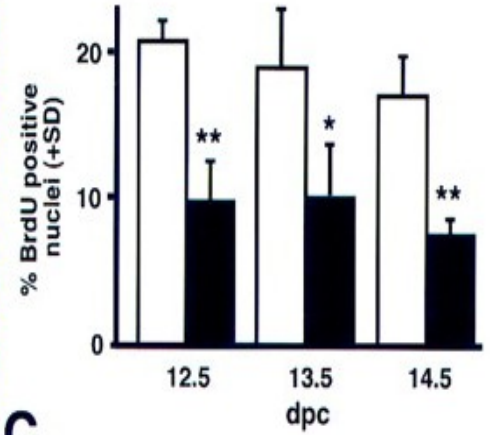
50% cell enlargement

Indian hedgehog (Ihh)

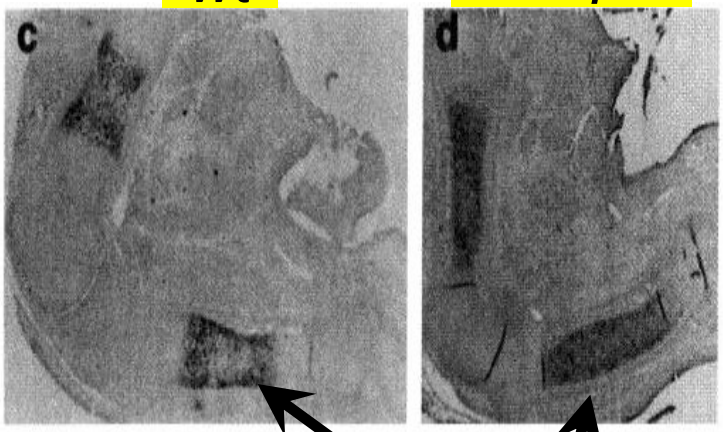




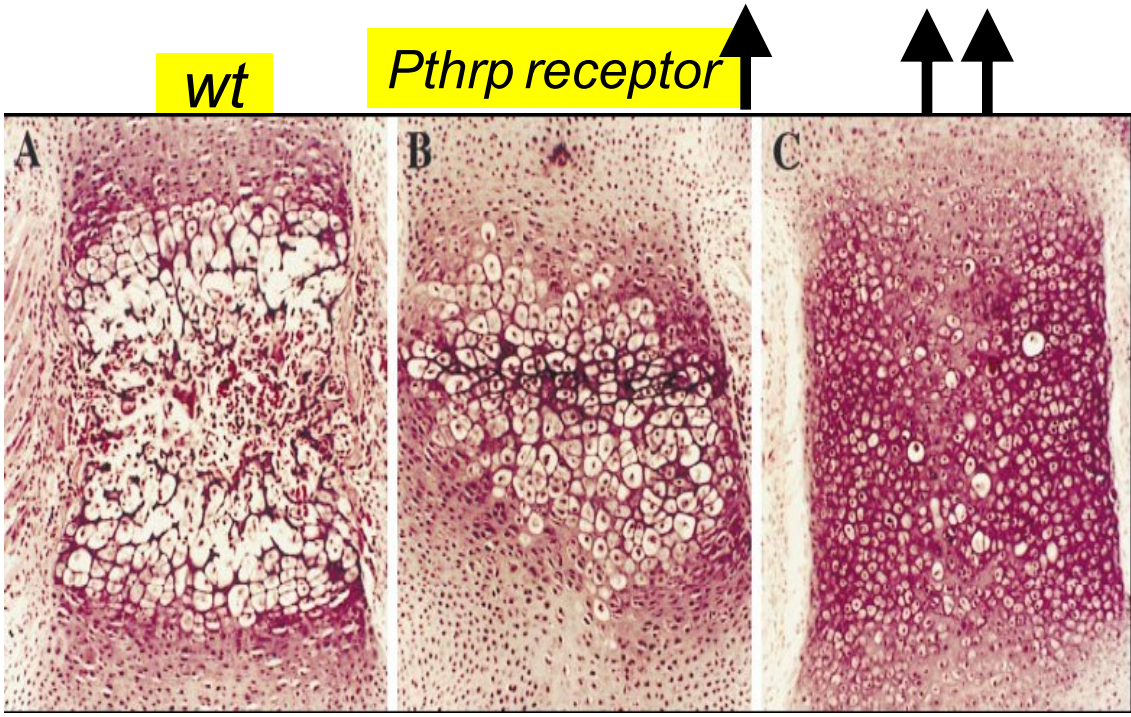




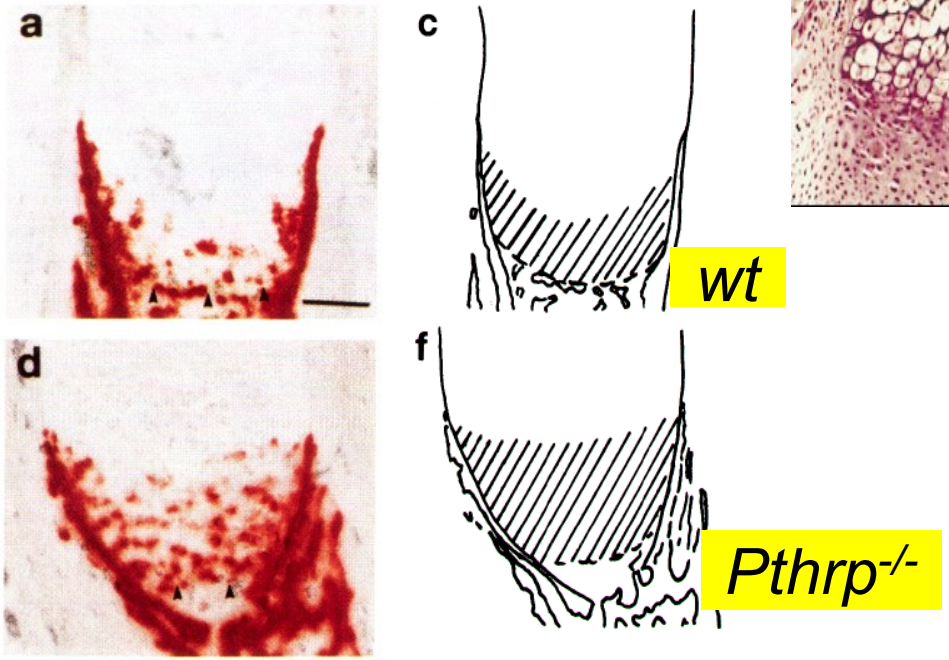
Parathyroid hormone-related peptide (PTHrP)

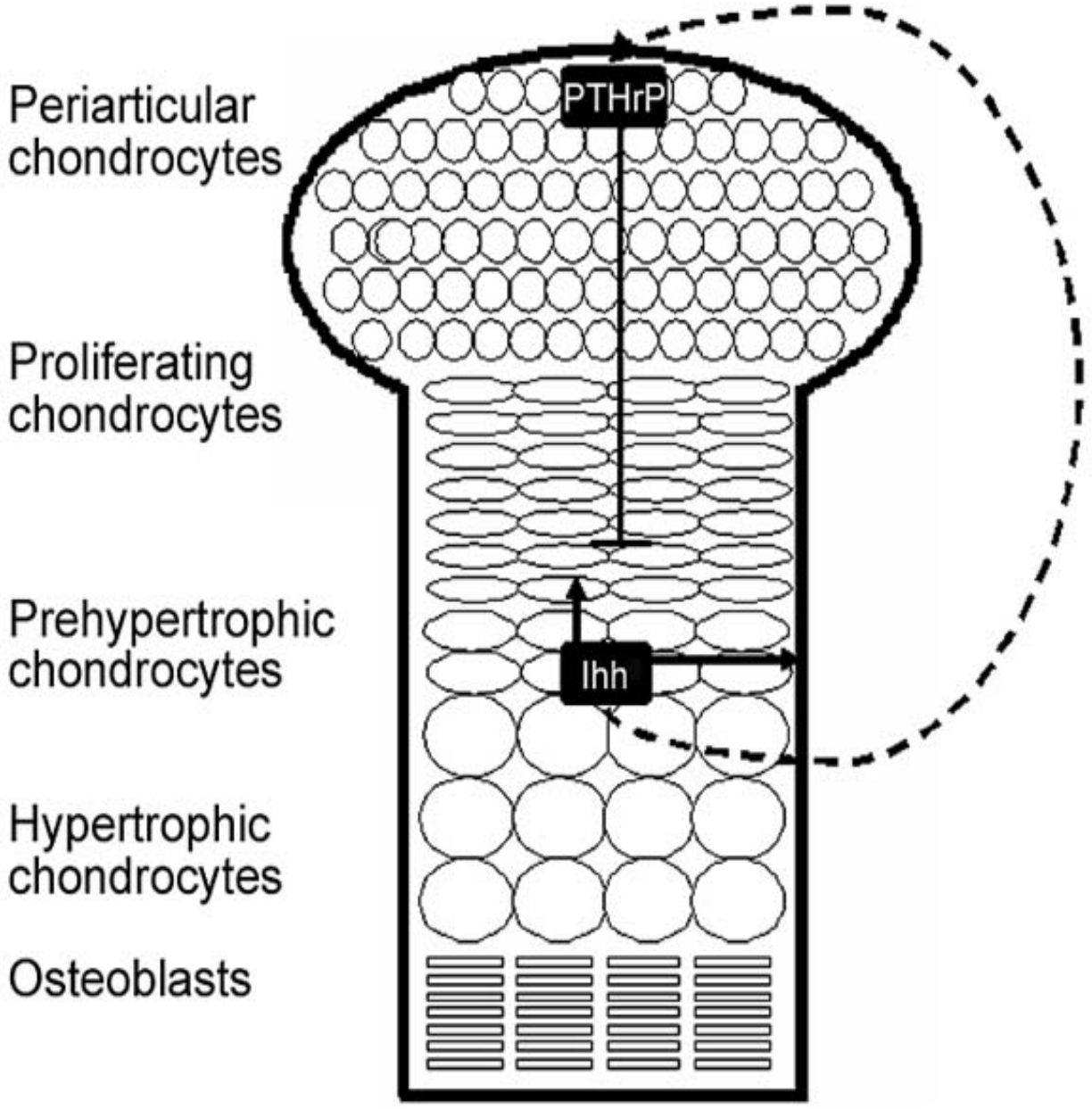


Coll type X in situ



Sternal cartilage




Periarticular chondrocytes
Proliferating chondrocytes
Prehypertrophic chondrocytes
Hypertrophic chondrocytes
Osteoblasts
PTHrP
Ihh

REGENERATION: Awakening of developmental pathways in adult organism.

AGING AND SENESCENCE: decline of physiological functions with age, leading to decreased ability to cope with stresses and increased susceptibility to diseases.

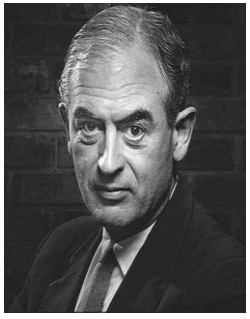
A part of developmental program or simply a result of wear and tear (drugs, alcohol, cigarets, woman)?

SENESCENCE IS UNDER GENETIC CONTROL

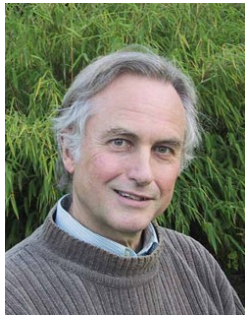
Longevity and time to attain reproductive maturity at puberty for various mammals

	Maximum life span (months)	Length of gestation (months)	Age at puberty (months)
Man	1440	9	144
Finback whale	960	12	—
Indian elephant	840	21	156
Horse	744	11	12
Chimpanzee	534	8	120
Brown bear	442	7	72
Dog	408	2	7
Cattle	360	9	6
Rhesus monkey	348	5.5	36
Cat	336	2	15
Pig	324	4	4
Squirrel monkey	252	5	36
Sheep	240	5	7
Gray squirrel	180	1.5	12
European rabbit	156	1	12
Guinea-pig	90	2	2
House rat	56	0.7	2
Golden hamster	48	0.5	2
Mouse	42	0.7	1.5

Mutation accumulation or Selfish genes or Antagonistic pleiotrophy or Disposable soma?



P. Medawar

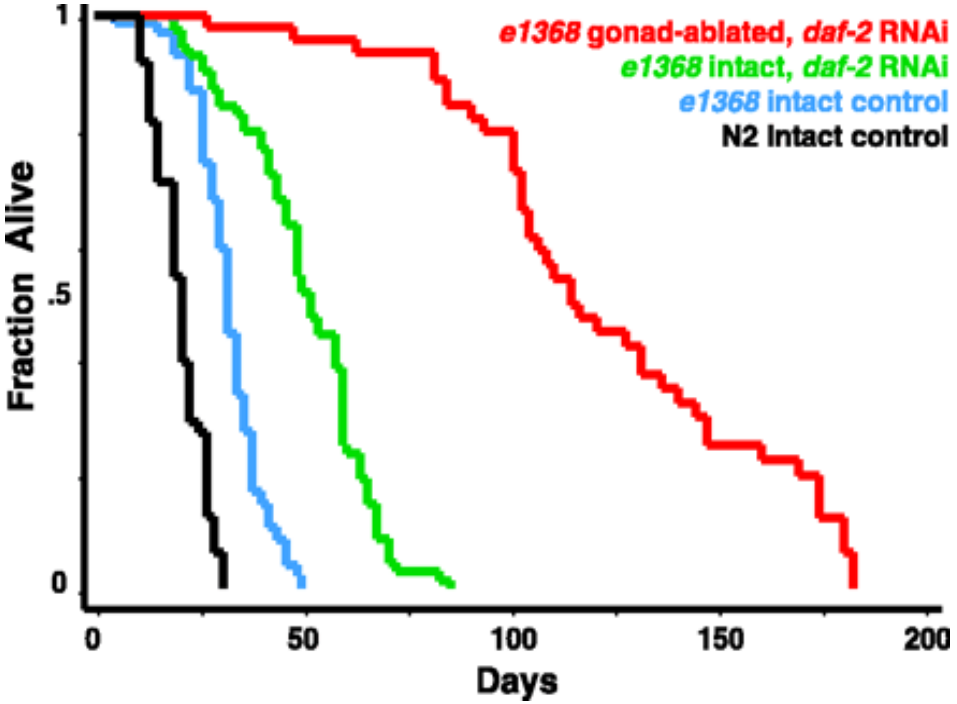


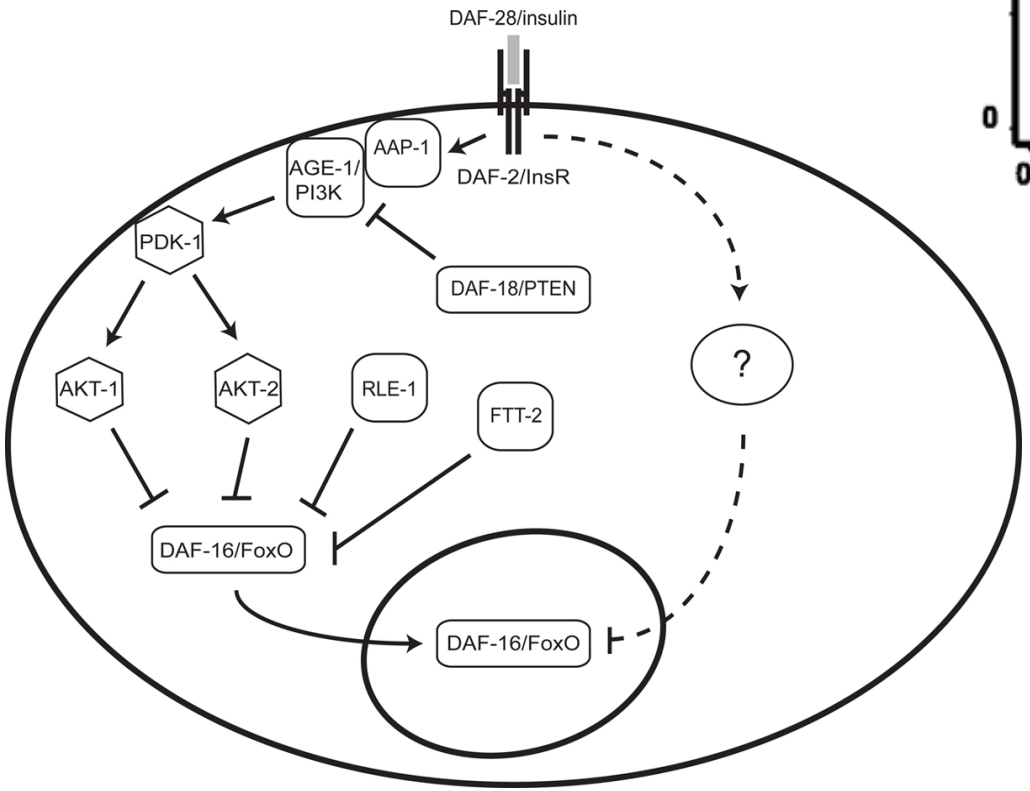
R. Dawkins

G. Williams

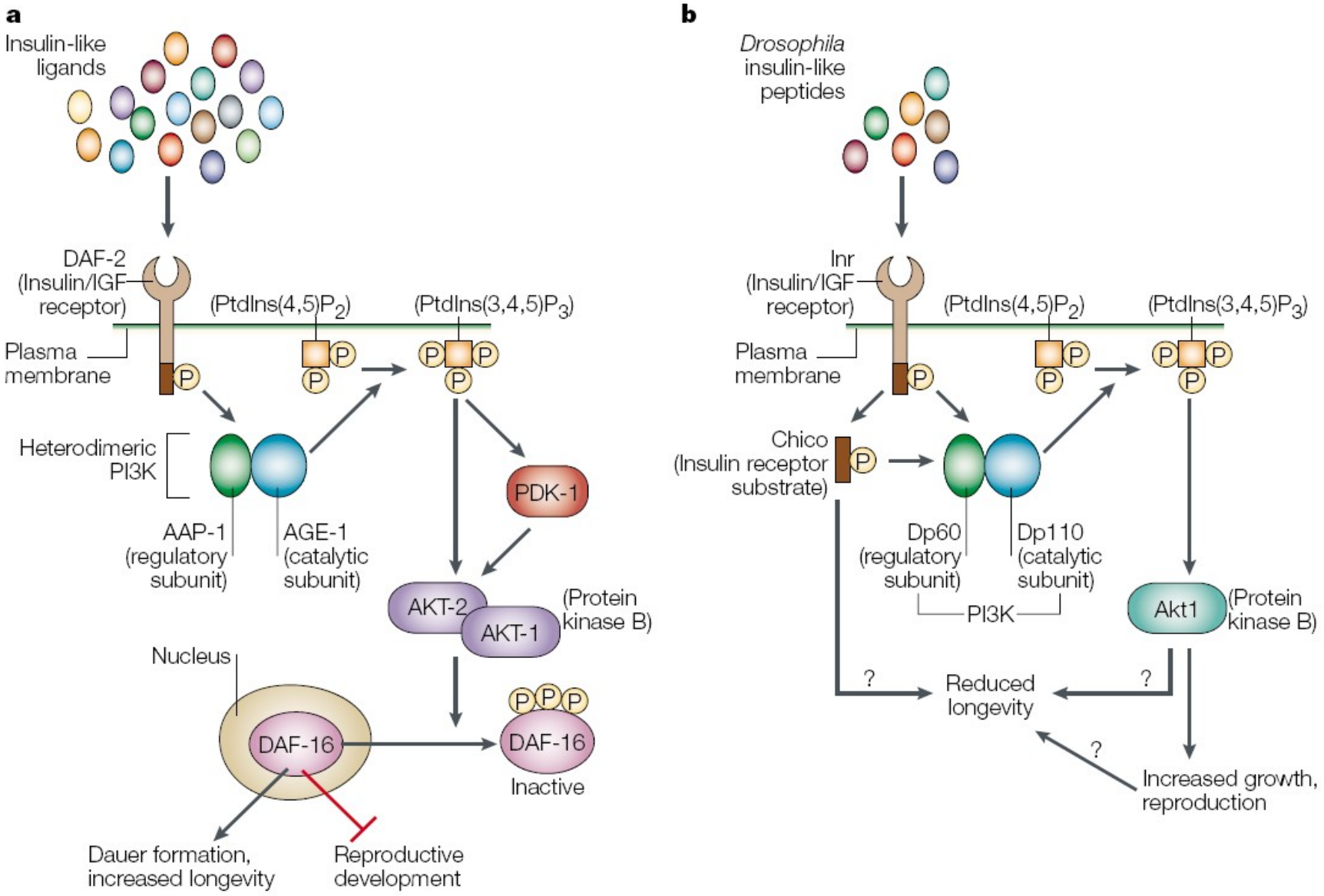
T. Kirkwood

GENES CAN ALTER THE TIMING OF SENESCENCE

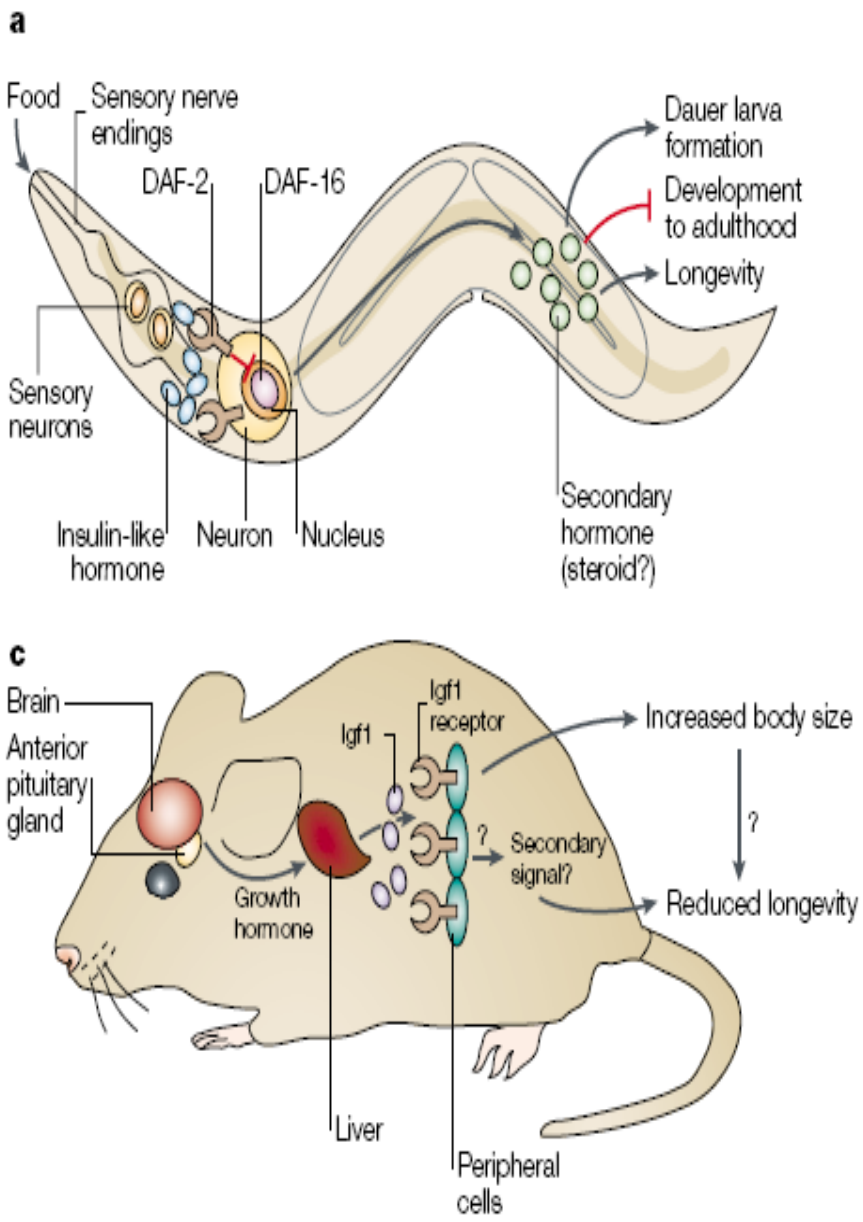




INSULIN/IGF SIGNALING IN *C. elegans* AND *Drosophila*



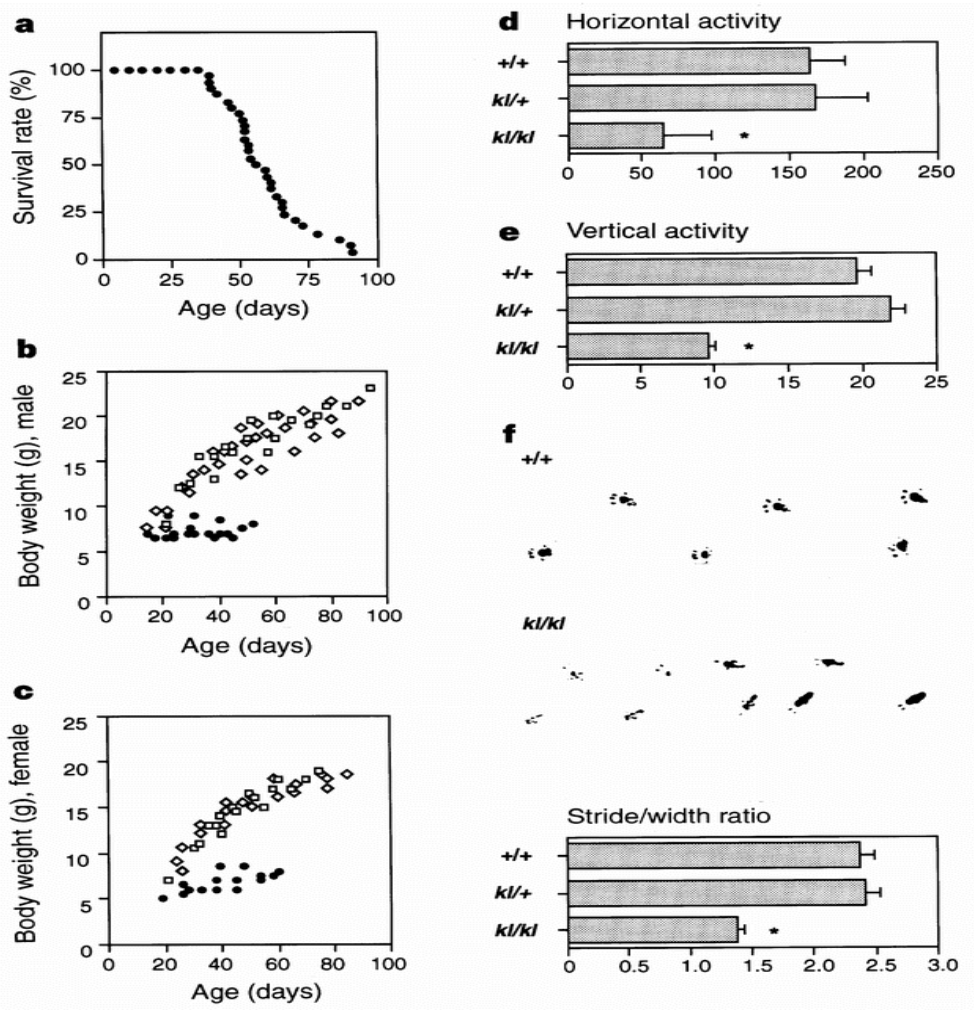
NEUROENDOCRINE REGULATION OF AGEING

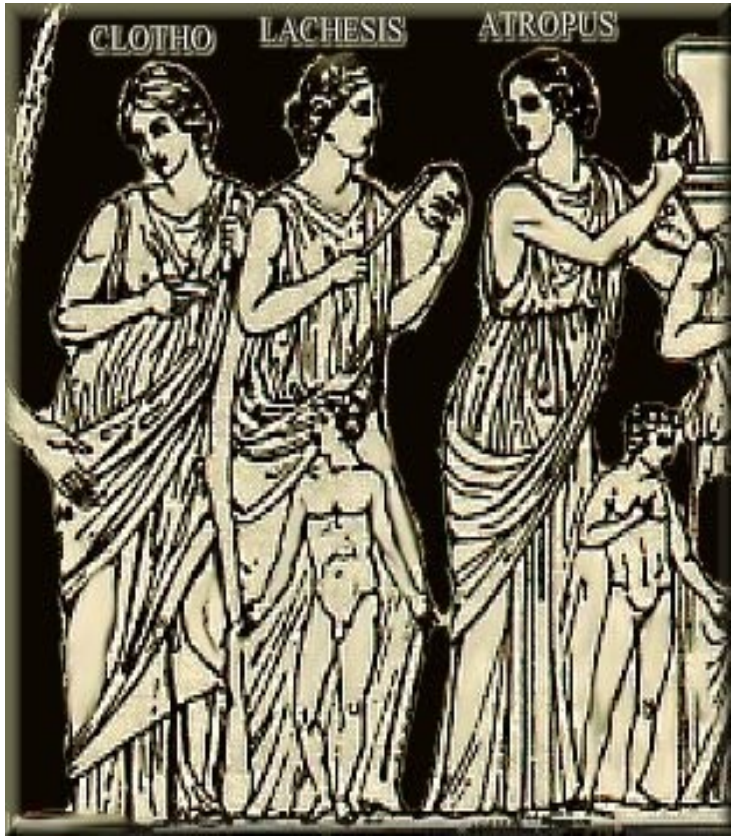


Mutation of the mouse *klotho* gene leads to a syndrome resembling ageing

NATURE | VOL 390 | 6 NOVEMBER 1997

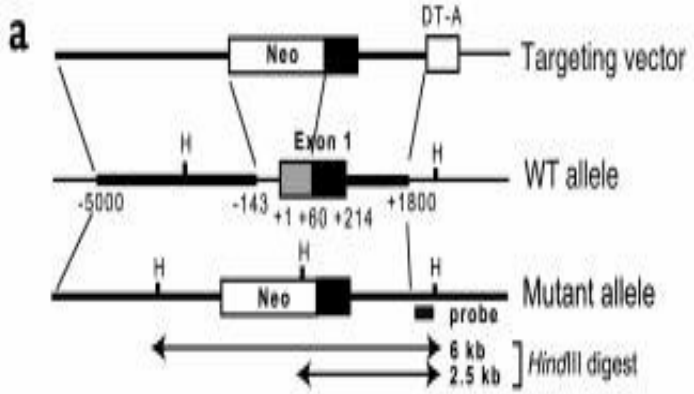
Makoto Kuro-o*, Yutaka Matsumura*†, Hiroki Aizawa*†, Hiroshi Kawaguchi‡, Tatsuo Suga†, Toshihiro Utsugi†, Yoshio Ohyama†, Masahiko Kurabayashi†, Tadashi Kaname§, Eisuke Kume‖, Hitoshi Iwasaki‖, Akihiro Iida¶, Takako Shiraki-Iida*¶, Satoshi Nishikawa#, Ryozo Nagai†* & Yo-ichi Nabeshima*†

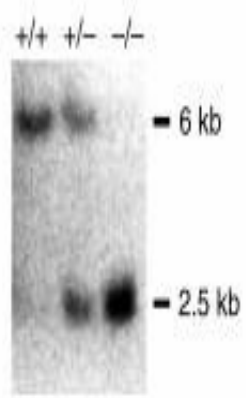


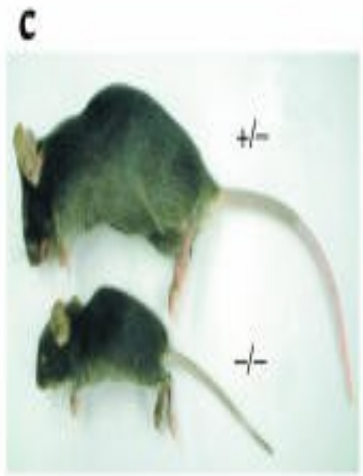


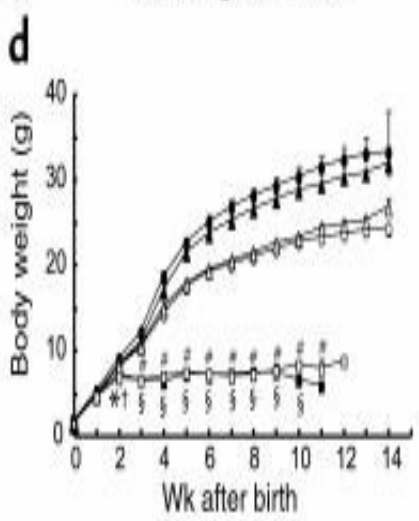
Targeted ablation of *Fgf23* demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism

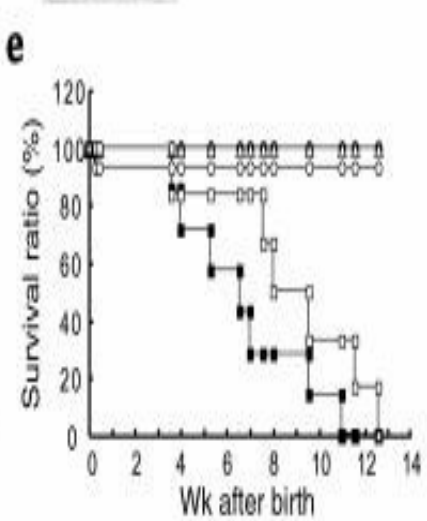
Takashi Shimada,[1] Makoto Kakitani,[1] Yuji Yamazaki,[1] Hisashi Hasegawa,[1]

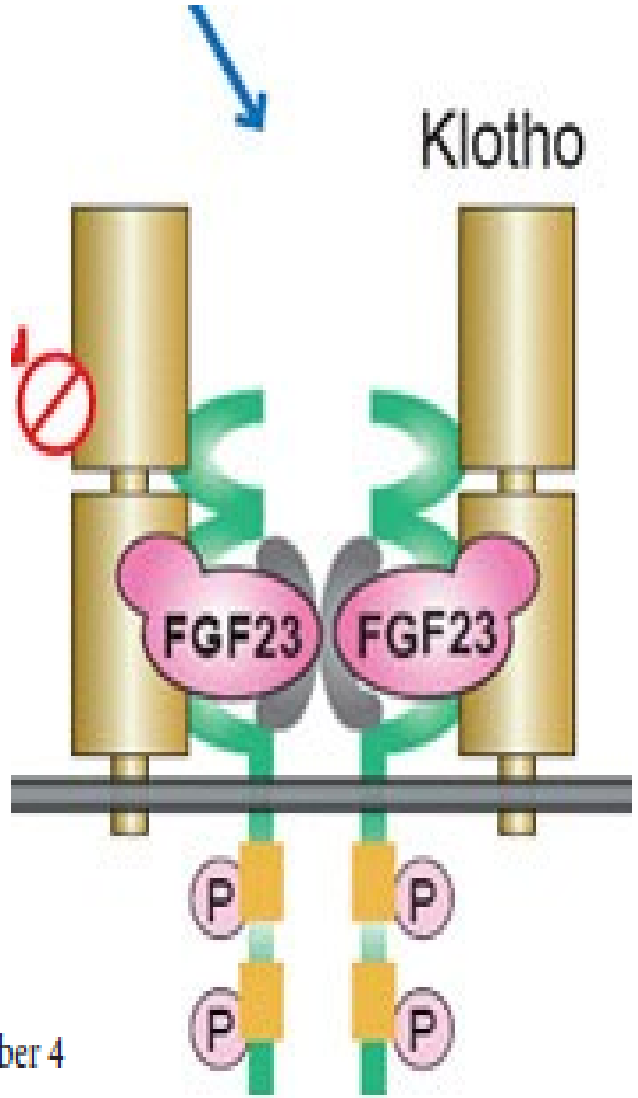






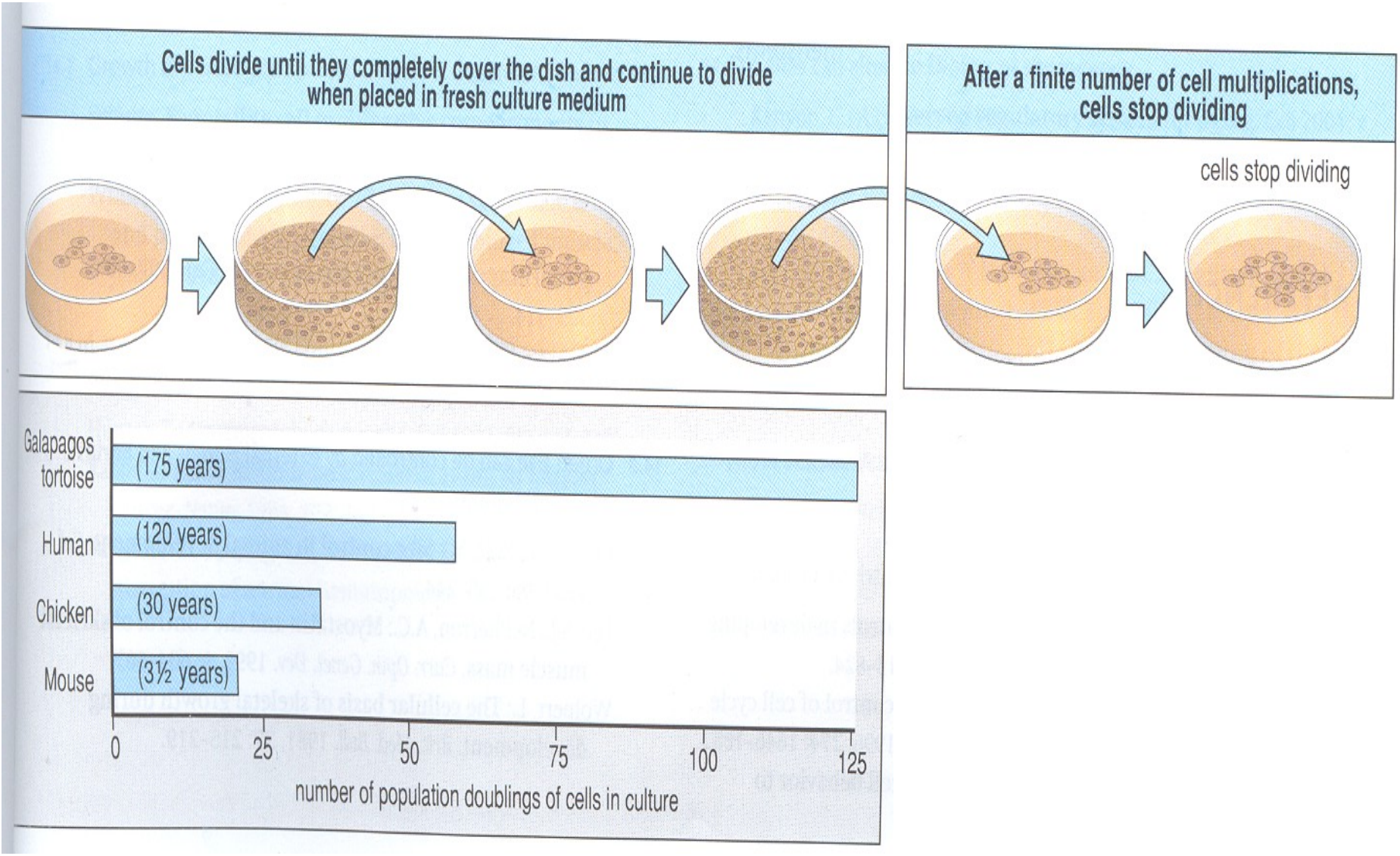


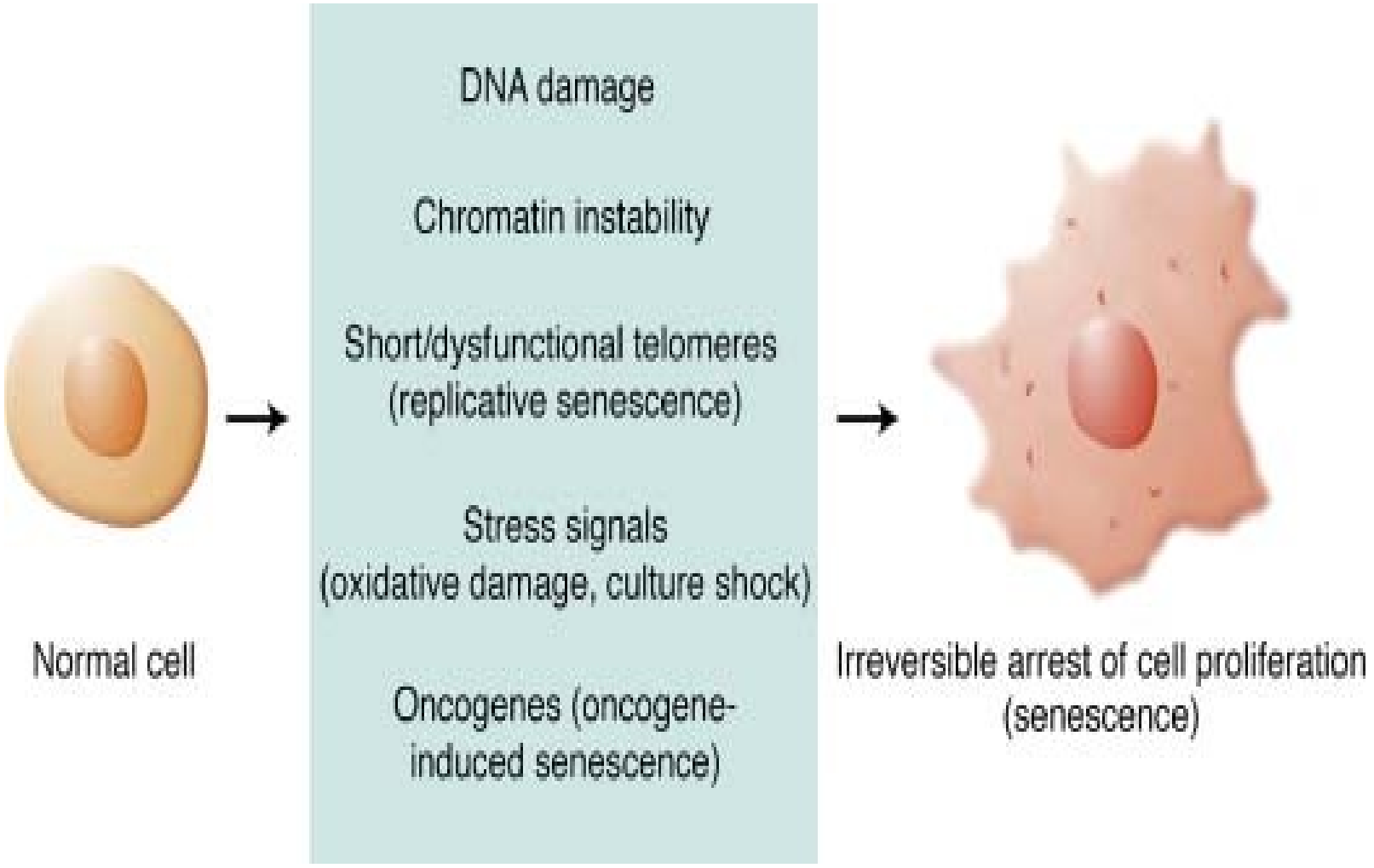




The Journal of Clinical Investigation | February 2004 | Volume 113 | Number 4

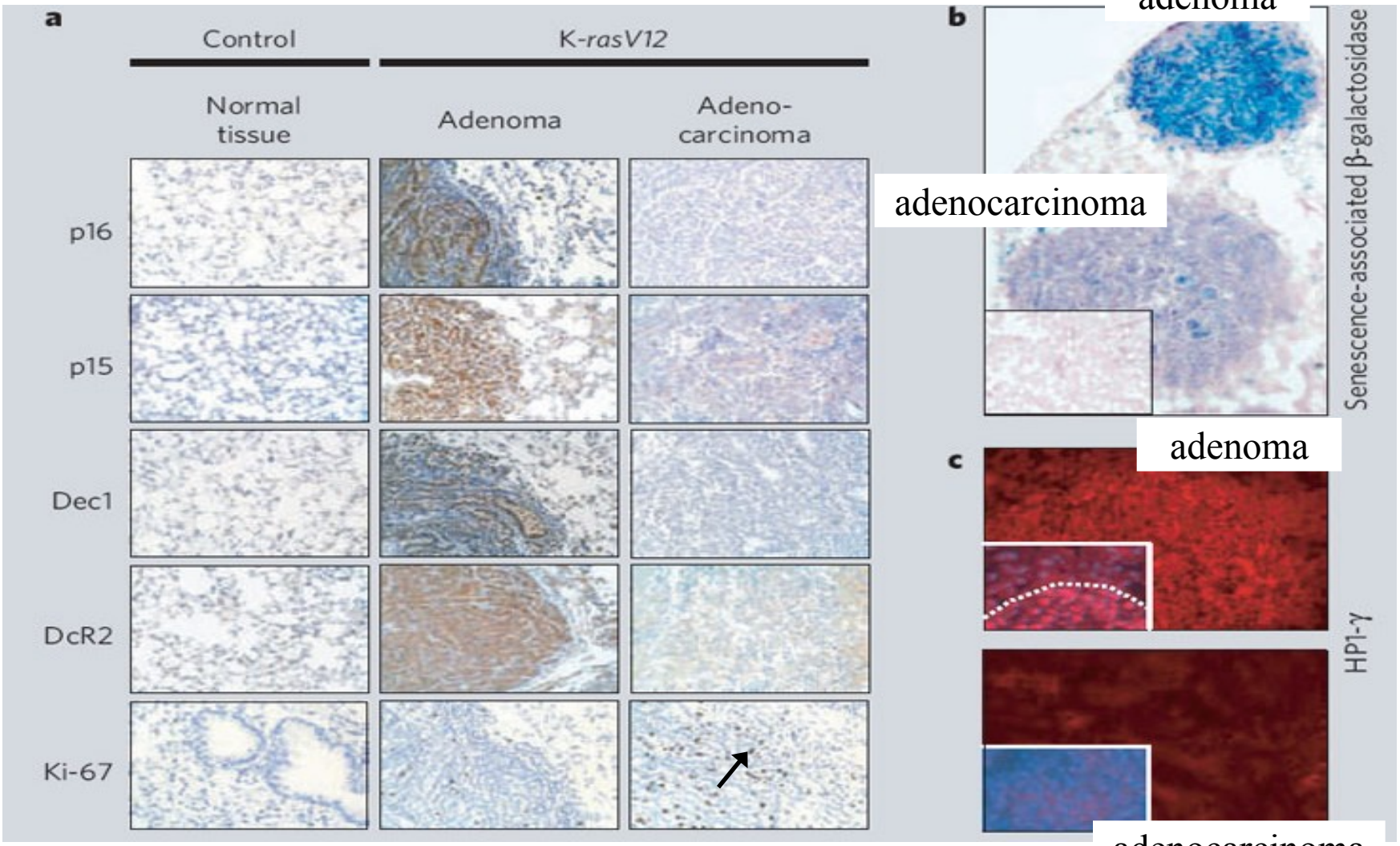
CELLULAR SENESCENCE: Irreversible growth arrest with no apoptosis. Cells are viable, functioning, but can not divide.



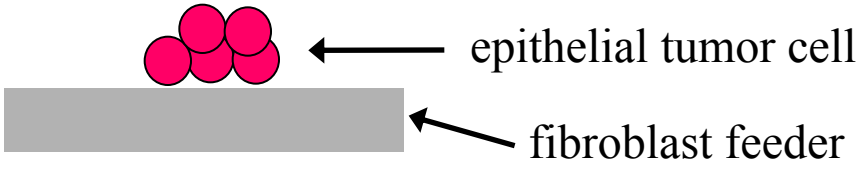

DNA damage
Chromatin instability
Short/dysfunctional telomeres
(replicative senescence)
Stress signals
(oxidative damage, culture shock)
Oncogenes (oncogene-
induced senescence)
Normal cell
Irreversible arrest of cell proliferation
(senescence)

ONCOGENE-INDUCED SENESCENCE AS A BARRIER TO TUMOR DEVELOPMENT

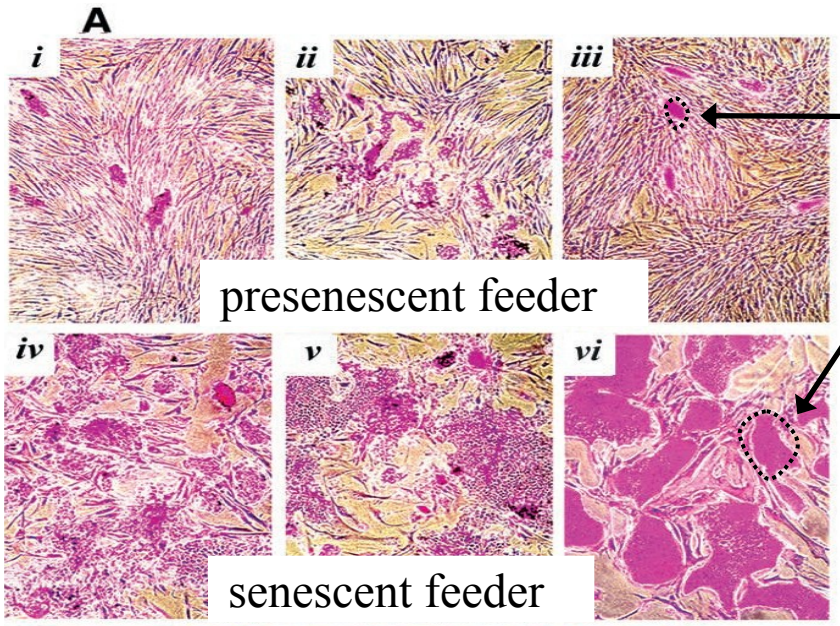
normal cell + oncogene (*rasV12*) → tumor
normal cell + oncogene (*rasV12*) → apoptosis
normal cell + oncogene (*rasV12*) → senescence

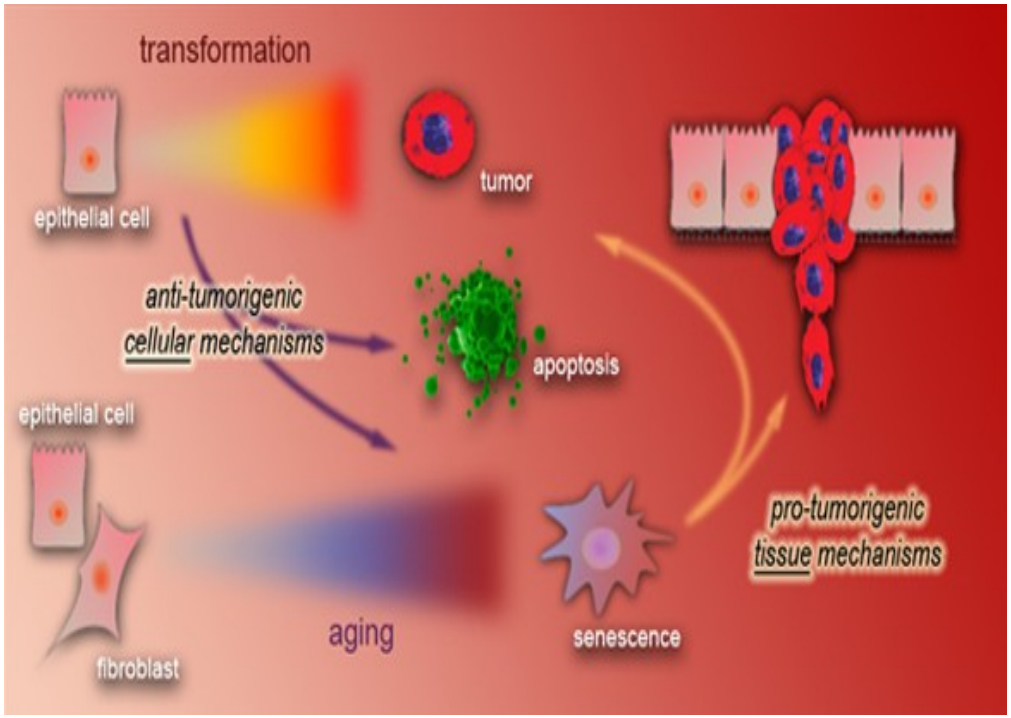


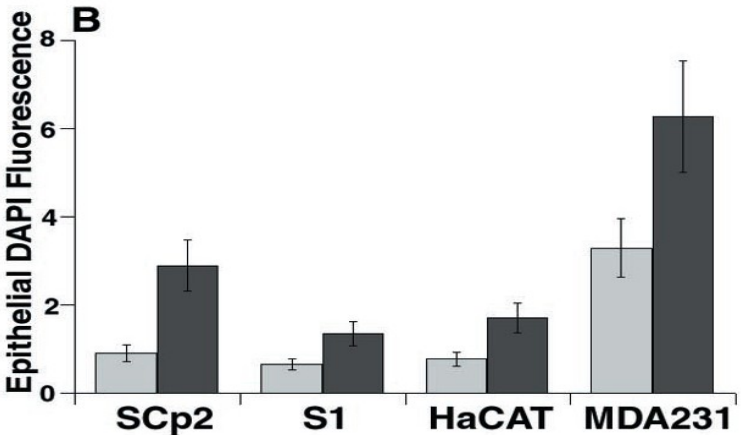
ANTAGONISTIC PLEIOTROPY



J. Campisi

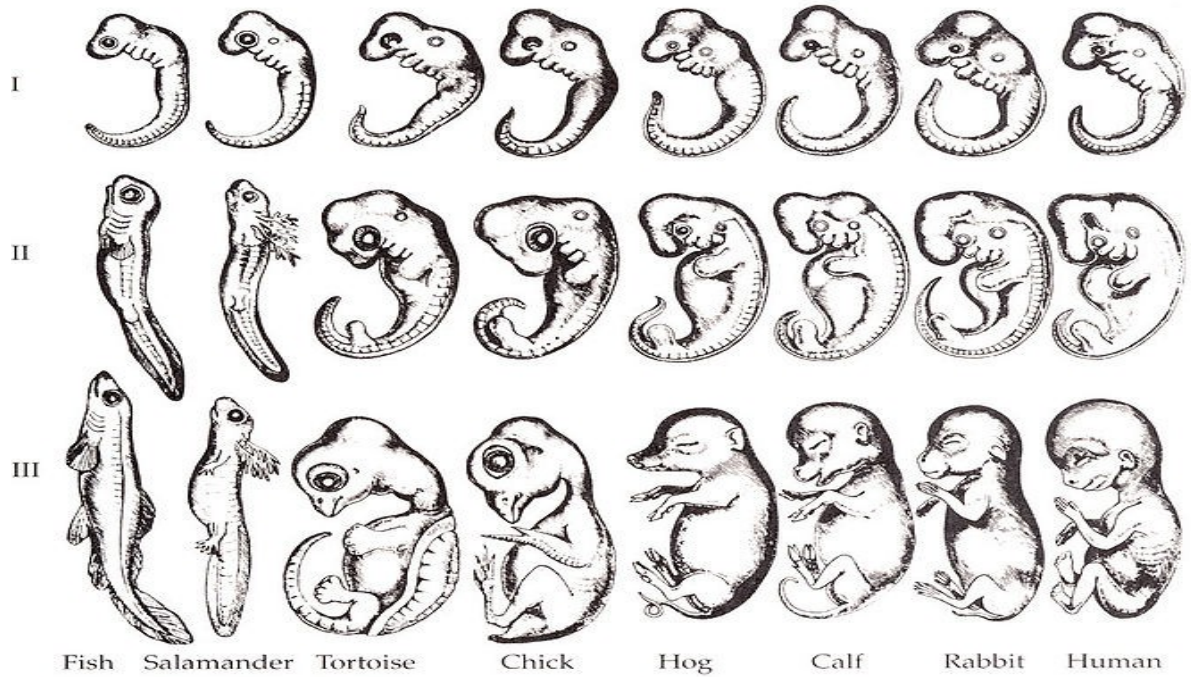






EVOLUTION AND DEVELOPMENT

Nothing in biology makes sense unless viewed in the light of evolution

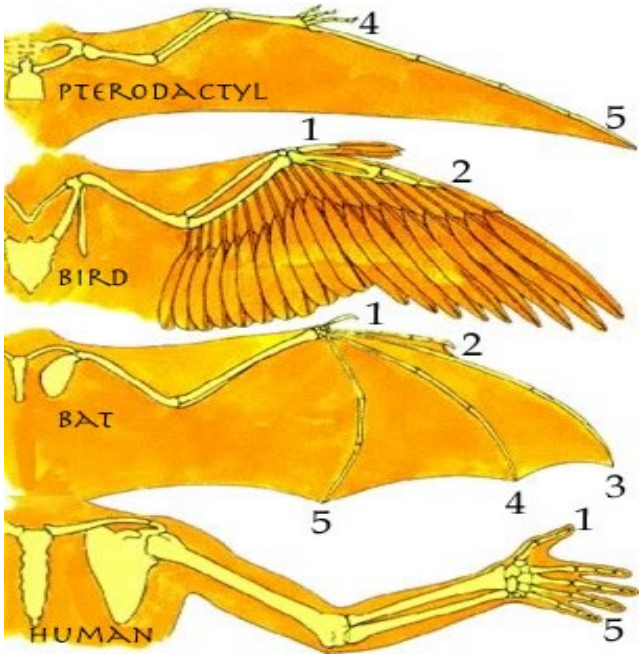


1. Ontogeny recapitulating the phylogeny: Haeckel 1869.
2. Neodarwinism: morphological changes appear gradually as a result of action of number of mutations each having a small effect. Changes arising from natural selection are called adaptive evolution or adaptation.
3. Most changes in DNA is not adaptive but neutral evolution, consisting of accumulation of mutations of no selective consequence that spread through the population from one generation to next (genetic drift).

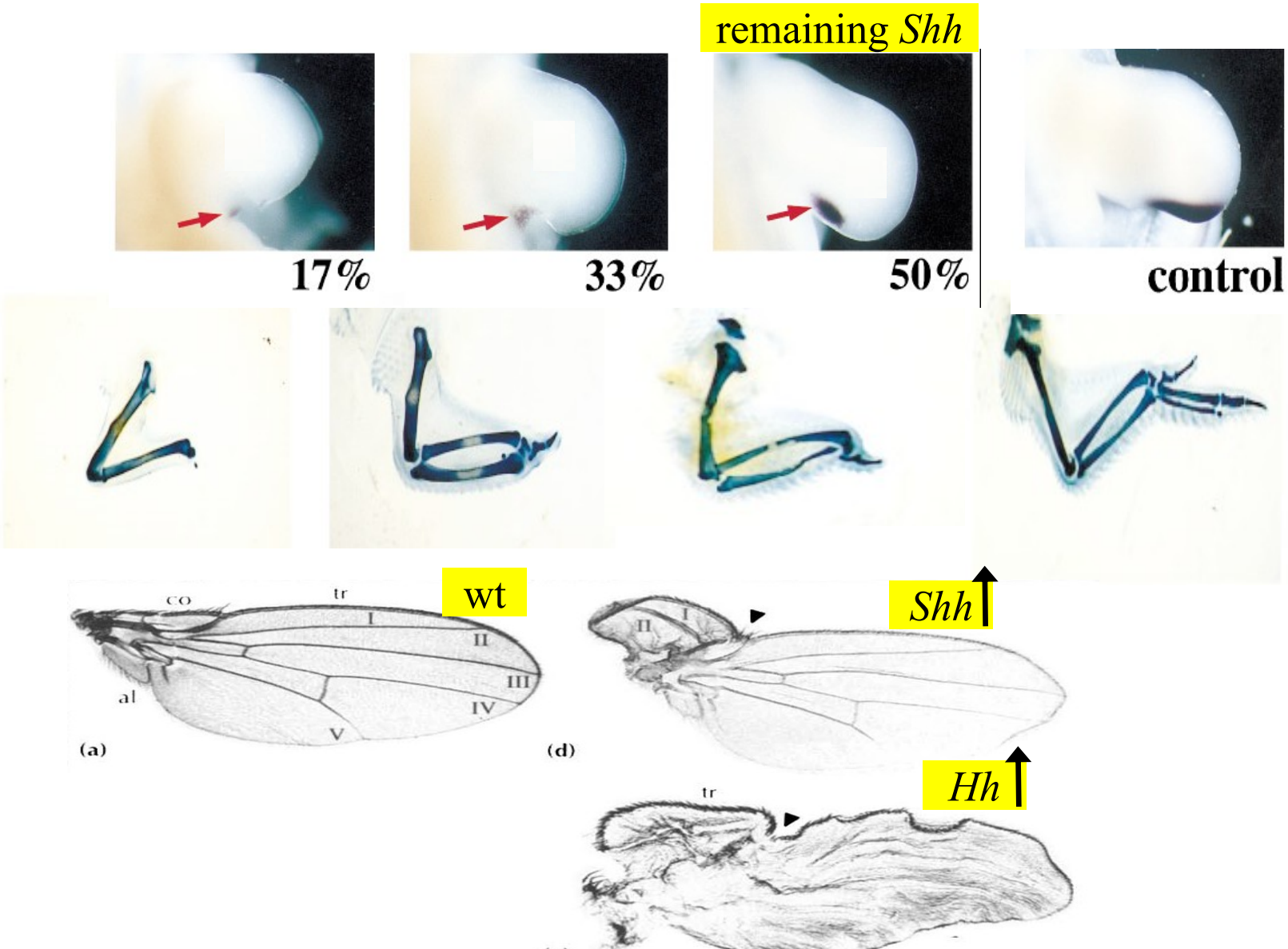
UNDERSTANDING OF DEVELOPMENT HELPS EVOLUTIONARY BIOLOGY TO ANSWER QUESTIONS THAT COULD NOT BE ANSWERED BEFORE

homology - structures that look similar and are descendent from a common ancestor

analogy - no common ancestry but the parts look similar because the natural selection forced a convergence of structure to meet the need for a similar function



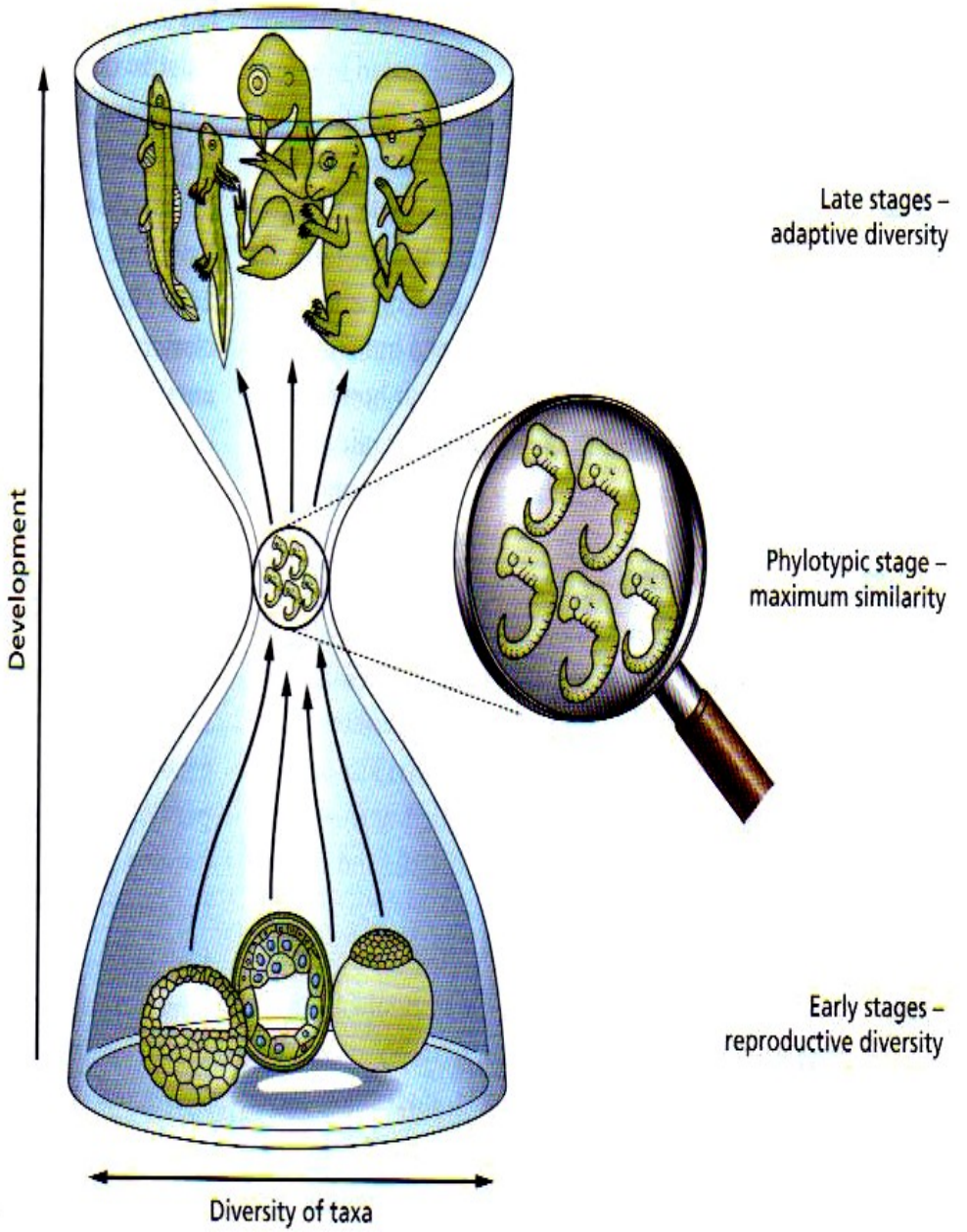
BUT THE GENES REGULATING DEVELOPMENT OF ANALOGOUS STRUCTURES ARE THE SAME



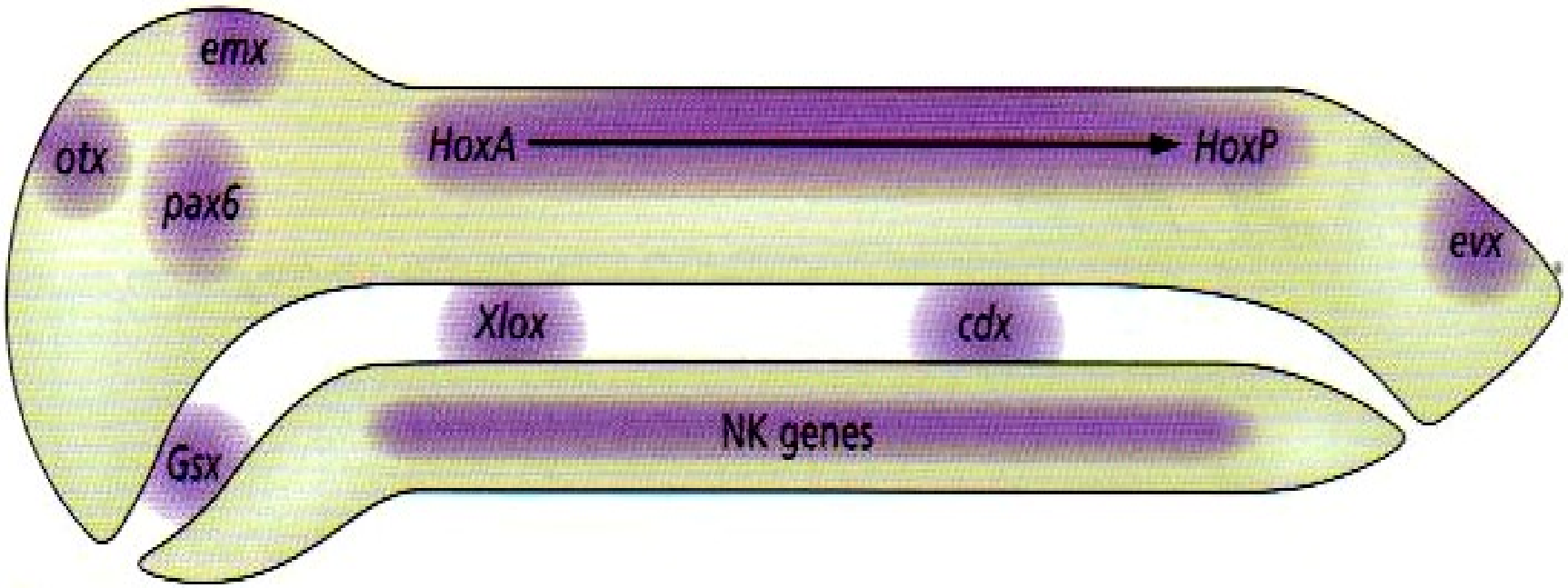
THE PRIMORDIAL ANIMAL

Body plan genes – genes that specify the features common to all animals**.**
Brachyury **-** expressed in differently shaped reagions in *Xenopus*, chick and mouse but they all correspond to what was previously a mesoderm. Thus the mesoderm is a real cell state definable by the expression of *brachyury*.

THE PHYLOTYPIC STAGE: A stage in development at which all members of taxon show maximal morphological similarity. Among vertebrates, the phylotypic stage is the **tailbud** stage when all vertebrates have a dorsal nerve cord, segmented somites, ventral heart, and a set of pharyngeal arches.



ZOOTYPE: Animal phyla = different body plans with no morhological homologies among them. Developmental biology now makes it possible to compare the expression patterns of key developmental genes between phyla. Some of theese seem to be conserved across the whole animal kingdom. They are active around the phylotypic stage for all the main animal groups examined. The totality of common expression domains is called the **zootype**. This cryptic anatomy of developmental gene expression patterns defines of what an animal actually is.



WHAT REALLY HAPPENED IN EVOLUTION can be seen by comparing the expression pattern of key developmental genes that give rise to two different morphologies, one ancestral and one derived.

Snakes, whales and flightless birds have lost limbs that their ancestors had. It is believed that the position of the limbs on the lateral plate is specified by the anteroposterior patterning systém of the whole body. This includes Hox genes but also the ParaHox and NK clusters. In the chick, *Hoxc6* and *Hoxc8* are expressed in the lateral plate between the two limb buds and repress limb formation in this region. In python that has no trace of forelimbs but a rudiment of hindlimbs, the *Hoxc8* and *8* expression extends all the way to the head but stops just short of the rudimentary hindlimbs.