What have we inherited, what do we share with our ancestors: the development of calciotropic hormones in the course of phylogenesis

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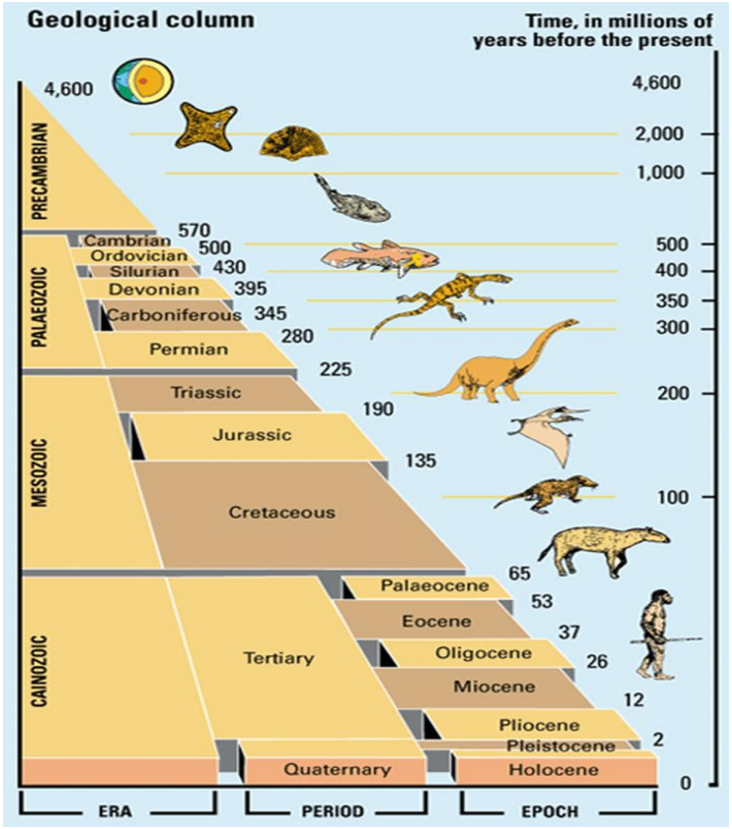
Evolution

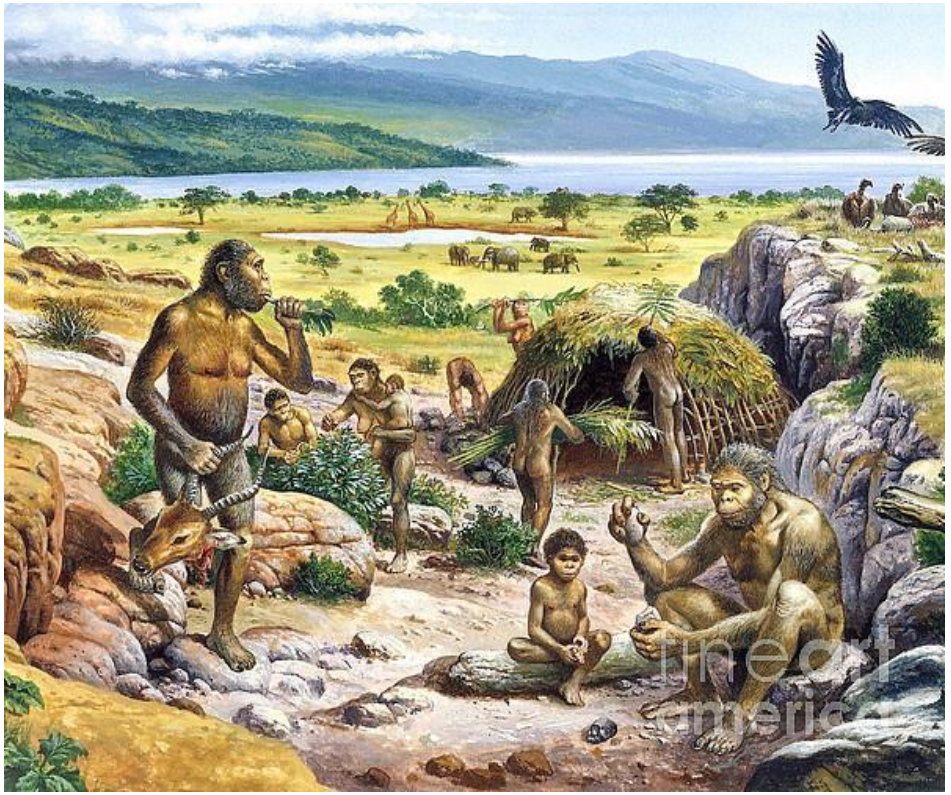
- Life moved from the sea to the land



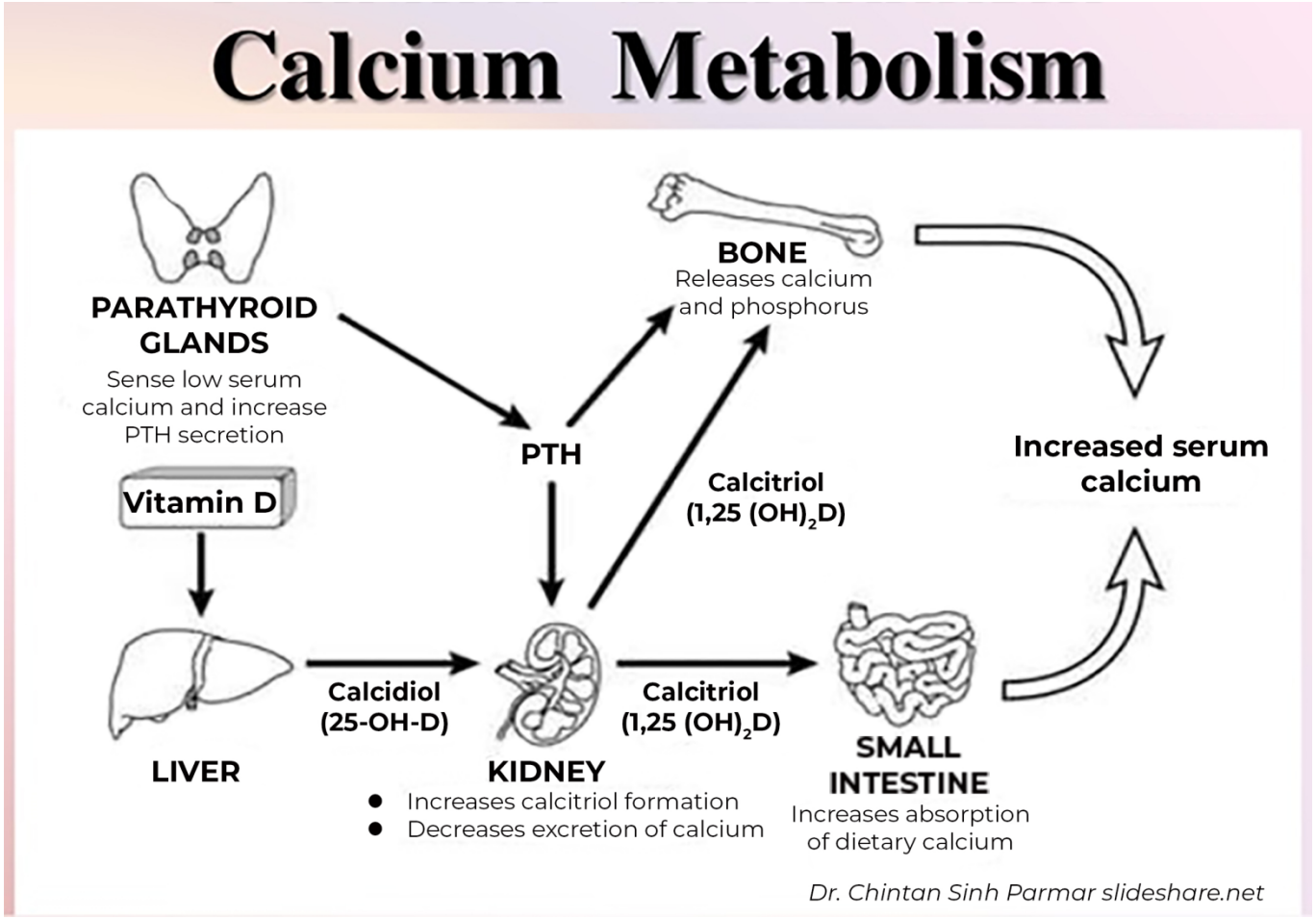



Evolution


Geological column
Time, in millions of years before the present
4,600
4,600
2,000
1,000
PRECAMBRIAN
570
Cambrian
500
Ordovician
430
Silurian
395
Devonian
345
Carboniferous
280
Permian
PALAEOZOIC
500
400
350
300
225
Triassic
190
Jurassic
135
Cretaceous
MESOZOIC
200
100
65
Palaeocene
53
Eocene
37
Oligocene
26
Miocene
12
Pliocene
2
Pleistocene
Tertiary
Quaternary
Holocene
CAINOZOIC
0
ERA
PERIOD
EPOCH

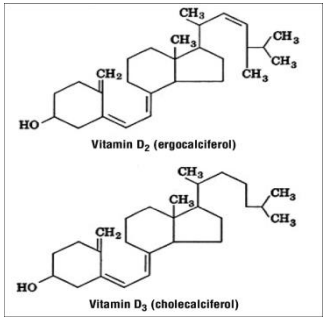


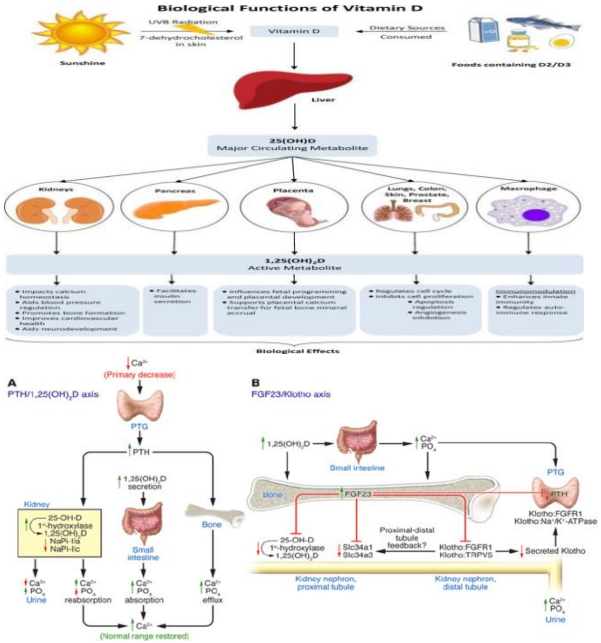
Skeleton
Ca/P metabolism



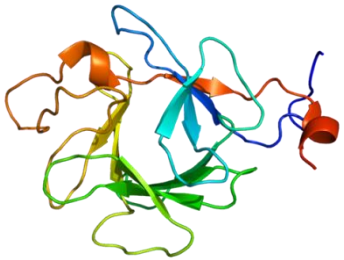
Skeleton
Essential calciotropic hormones

- Vitamin D

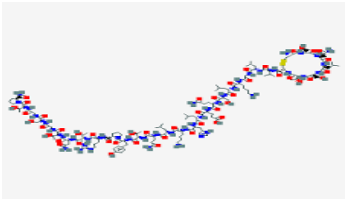


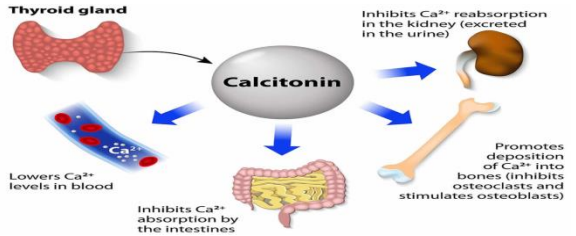


- FGF23

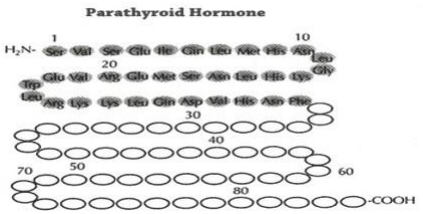


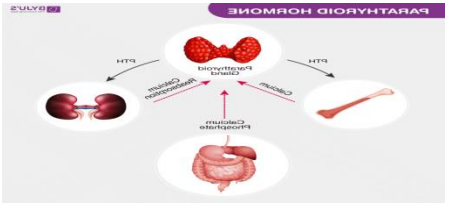
- Calcitonin





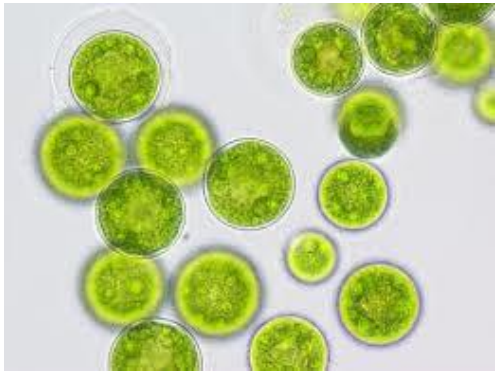
- PTH

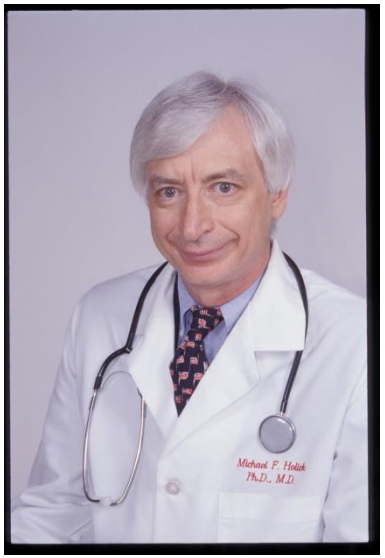




Vitamin D

- Vitamin D : photosynthesized in all organisms from the phytoplankton to mammals.
- Microalgae contain both vitamin D3 and provitamin D3, 7-dehydrocholesterol
- Vitamin D2 is produced in fungi and yeasts after UVB radiation .
- Vitamin D3 and its provitamin is present in leaves Solanaceae family of trees, shrubs, and herbs
- Functions of vitamin D in either phytoplankton or zooplankton remain unknown.
- Provitamin D evolved to protect UVR-sensitive macromolecules from solar UV damage or in regulating membrane permeability to cations, such as calcium?



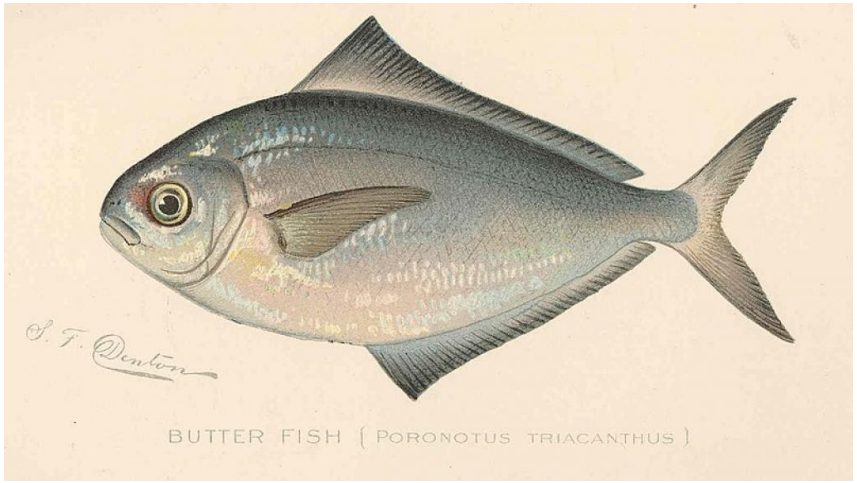


Hochberg Z et al Evolutionary Perspective in Rickets and Vitamin D. Front. Endocrinol. 2019; 10:306

Holick MF. Vitamin D: a millenium perspective. J. Cell. Biochem. 2003; 88:296–307.

Vitamin D

- Fish have the utmost natural content of vitamin D: they consume plankton which is rich in vitamin D and is the basis for the entire marine food web.
- Terrestrial animals have a calcified skeleton and lay eggs with a calcified shell; therefore they need provitamin D for calcium and bone metabolism.



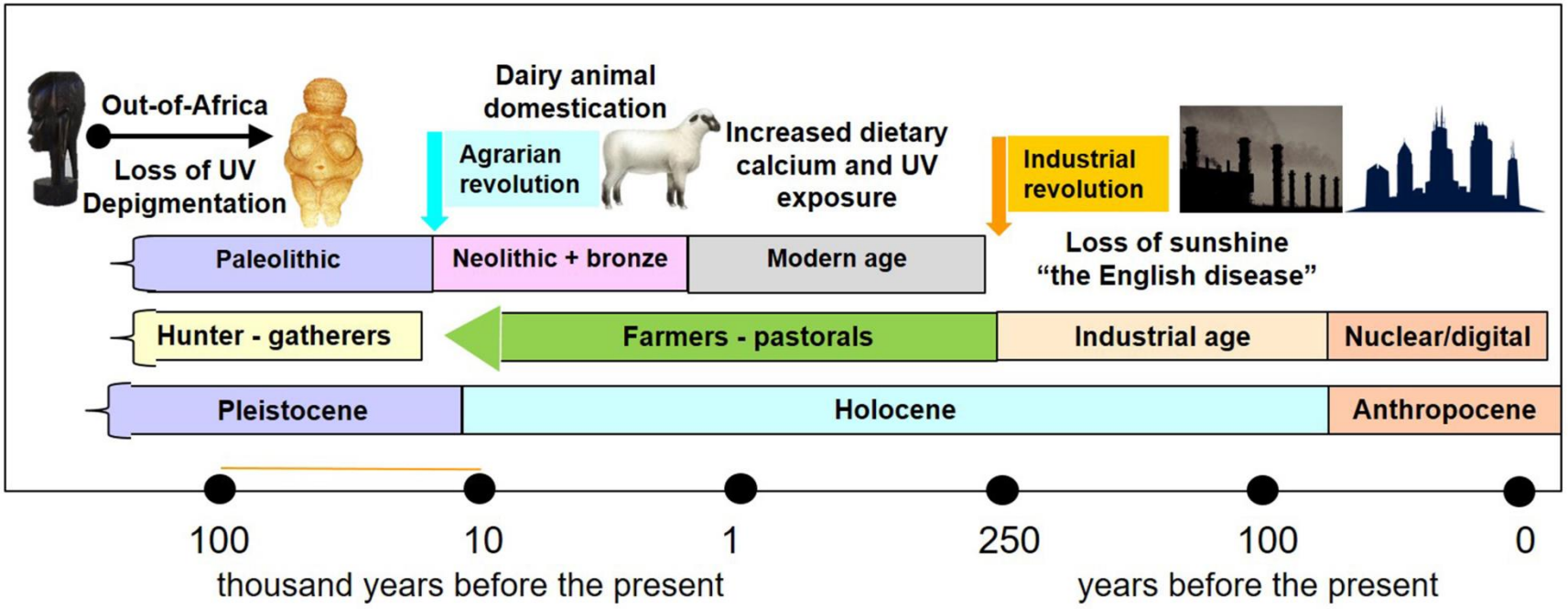
Vitamin D and humans

- Tropics – plenty of sunshine – plenty of vitamin D
- A high amount of dark melanin in the skin slows cutaneous synthesis of vitamin D3.
- Dark-skinned individuals require a six-time longer exposure to sunlight than fair-skin individuals to achieve the same vitamin D serum levels.
- When hominines left the forest for the sun-exposed savannah, they lost their fur, acquired a sweating mechanism, and their skin became pigmented to protect them from the higher levels of UVR.
- When H. sapiens migrated out of Africa, they received significantly less UVB radiation, and their skin depigmented to a degree that permitted UVB-induced synthesis of provitamin D3.
- A selective sweep of the promoter of the vitamin D receptor (VDR) happened as soon as *Homo sapiens* migrated out of Africa; it co-adapted with skin color genes to provide adaptation to latitudes and the levels of exposure to ultraviolet (UV)B radiation along the route out of Africa.

Hochberg et al, 2019

Vitamin D

Hochberg et al, 2019.

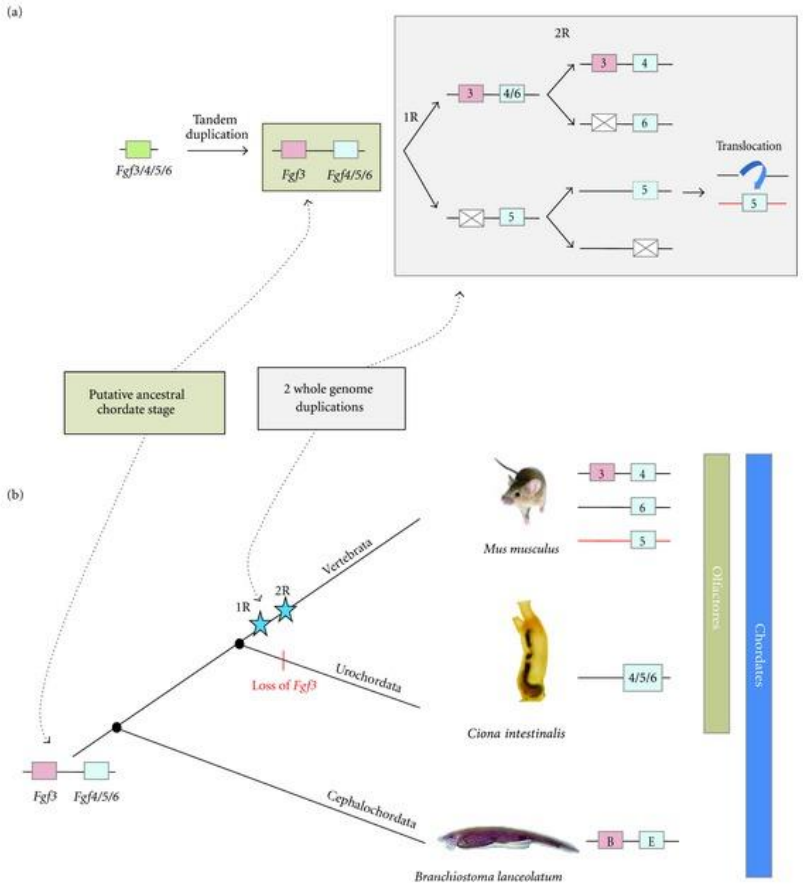


FGFs

- Fibroblast Growth Factors (FGFs) are small proteins (17-34 kDa) generally secreted, acting through binding to transmembrane tyrosine kinase receptors (FGFRs).
- Activation of FGFRs triggers several cytoplasmic cascades leading to the modification of cell behavior.
- FGFs play critical roles in a variety of developmental and physiological processes.
- Since their discovery in mammals, FGFs have been found in many metazoans and some arthropod viruses.
- FGF23 play a key role in phosphate and bone metabolism

FGF family

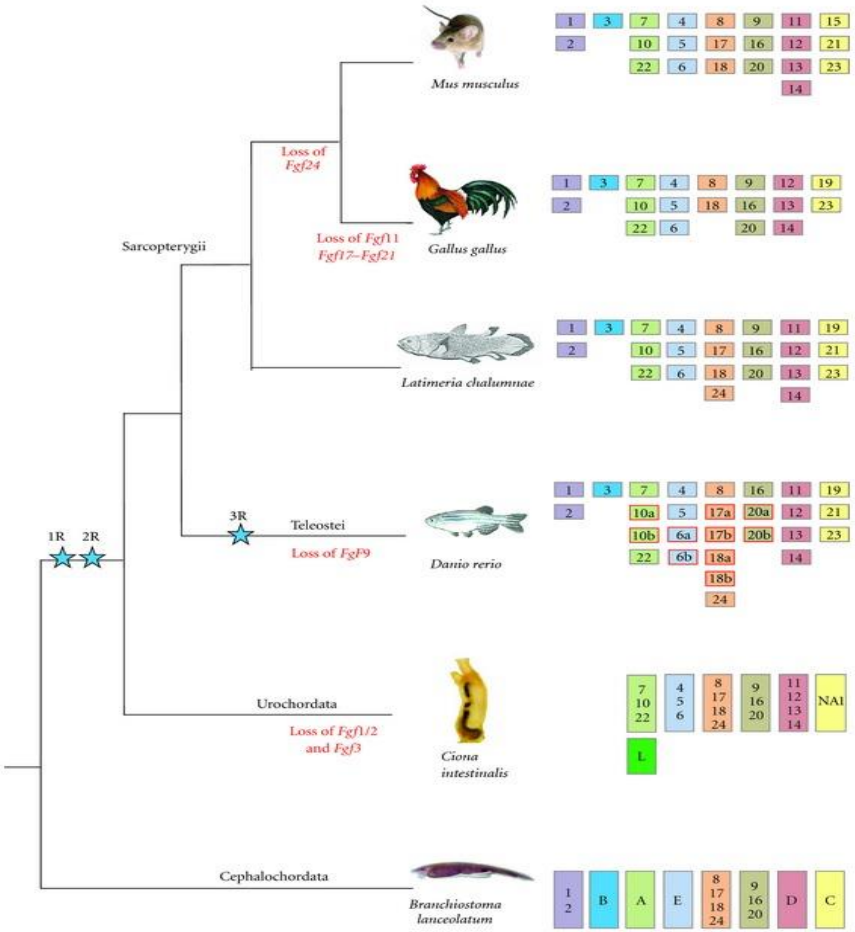
- 8 subfamilies
- Initially discovered in mammals (6 subfamilies)
- FGF gene studies
- Ancestral FGF gene (named FGF3/4/5/6) was duplicated in tandem before chordate diversification.



Oulion S et al. Evolution of the FGF Gene Family Int J Evolution Biol 2012

FGF 23

expressed in fish → onwards

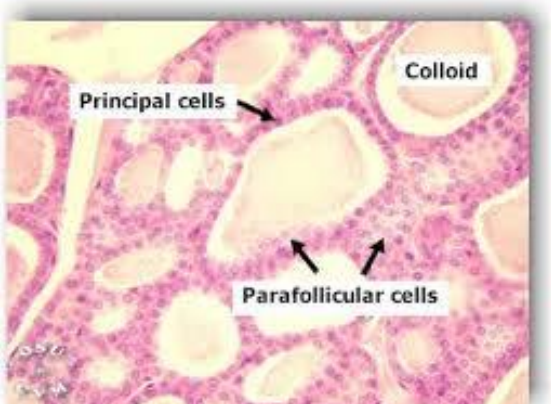


Calcitonin

protective role against hypercalcemia

- Calcitonin (CT) is synthesized by:
- the parafollicular cells (C-cells) associated with the ultimobranchial gland in lower vertebrates (fish i.e.Salmon)
- the parafollicular cells (C-cells) of the thyroid gland in mammals
- C-cells are derived from the neural crest and migrate forward to localize in the ultimo-branchial body in lower vertebrates and as parafollicular cells in man and related species

Wimalawansa SJ 2010



Calcitonin

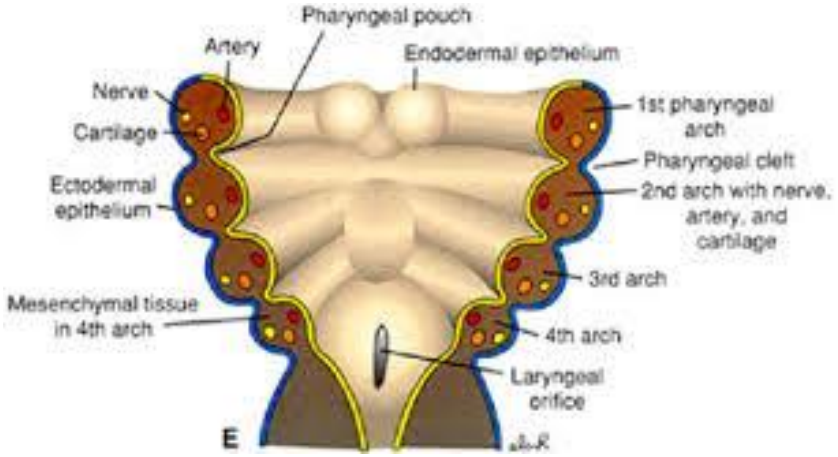
- CT is present in ocean fish which live in a high calcium environment with the need to expel calcium.
- CT is older than parathyroid hormone (PTH) which was first recognized in early land-dwelling animals when conservation rather than expulsion of calcium became important.
- An immunoreactive-human calcitonin (i-CT)-like molecule has been demonstrated in the nervous system of protochordates and cyclostome myxine (hagfish), in neural ganglia of Ciona intestinalis, an immediate ancestor of the vertebrate, but lacking a skeleton and in the ultimobranchial body of the amphibian, Rana

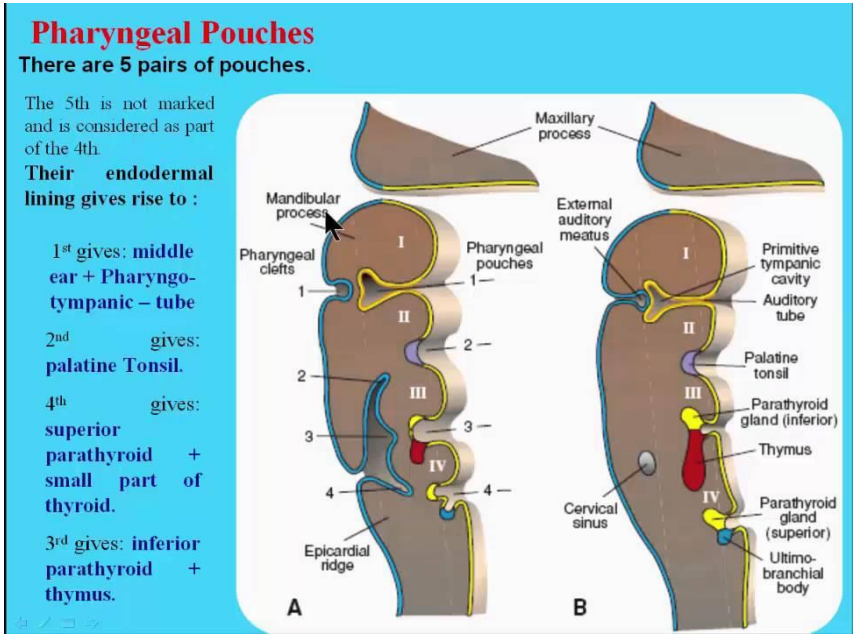
Wimalawansa SJ 2010

PTH

- Paradigm: Parathyropid glands and parathyroid hormone (PTH) evolved with the emergence of the tetrapods, reflecting a need for new controls on calcium homeostasis in terrestrial, rather than aquatic, environments.
- The parathyroid gland is derived from the pharyngeal pouch endoderm under the control of a key regulatory gene, *Gcm-2*. forming parathyroid gland
- *BUT:*
- *Gcm-2* is present not only in tetrapods but also in teleosts and chondrichthyans, and that in these species, *Gcm-2* is expressed within the pharyngeal pouches and internal gill buds that derive from them in zebrafish (*Danio rerio*), a teleost, and dogfish (*Scyliorhinus canicula*), a chondrichthyan.

Okabe M et al. The origin of PTH gland PNAS 2004;101: 17716-17719;





PTH

- *Gcm-2* is required for the formation of the internal gill buds in zebrafish.
- PTH -encoding genes exist in fish (zebrafish, dogfish) and show that these genes are expressed by the gills.
- The gills express the calcium-sensing receptor, which is used in tetrapods to monitor serum calcium levels.
- Tetrapod parathyroid gland and the gills of fish are evolutionarily related structures.
- The parathyroid likely came into being as a result of the transformation of the gills during tetrapod evolution.

- Okabe M et al. The origin of PTH gland PNAS 2004;101: 17716-17719;

So, it was a long way to go…..
..to achieve a complex skeleton