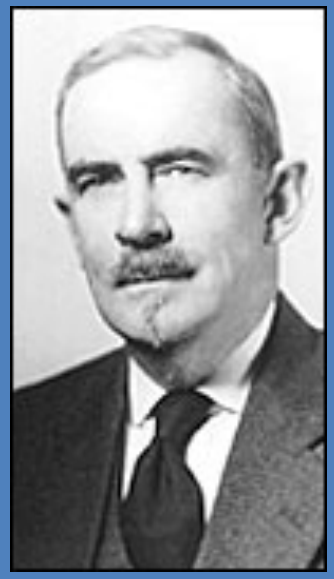
THE 2011 WILLIAM ALLAN AWARD of THE AMERICAN SOCIETY of HUMAN GENETICS to The Right Person "J.M. Opitz"?



Dr. William Allan
1881 – 1943

Medical Genetics (Pediatrics),
Human Genetics,
Pathology,
Obstetrics & Gynecology

University of Utah School of Medicine
Salt Lake City, Utah

61st Annual Meeting
American Society of Human Genetics
&
XII International Congress of Human Genetics
Montréal, Canada
October 11 – 15, 2011

THE WILLIAM ALLAN AWARD 2011

(To the right person?)

Possible explanations:

- Acute collective madness?
- A case of mistaken identity?

THE WILLIAM ALLAN AWARD 2011

Letter from a great man declining an award:

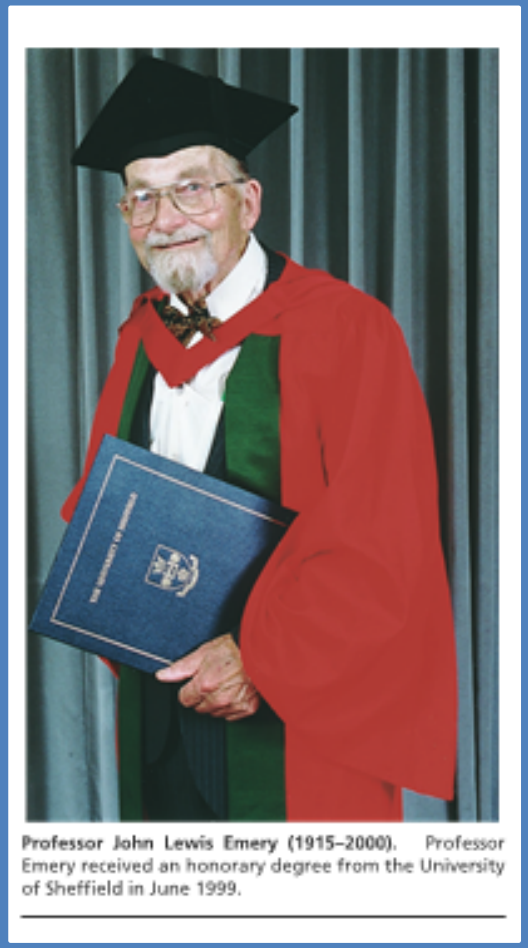
"I am extremely sorry not to be with you all. As you will probably appreciate, things like being honored are not my cup of tea"

John

DOMINE NON SUM DIGNUS…

Paraphrase of John L. Emery:

Honors are not my cup of tea either, but I am glad to be here today with you all, with profound gratitude for the honor you have bestowed on me…happily pre- rather than postmortem.



Professor John Lewis Emery (1915–2000). Professor Emery received an honorary degree from the University of Sheffield in June 1999.

AN AMAZING GRACE*

- Family and friends along the way
- Patients and their families
- Fellow-students and fellow-humanists in Europe, Asia, the Americas…
- Fellow-staff and faculty in Iowa, Wisconsin, Montana, Idaho, Utah

*Unmerited and undeserved

STRANGENESS OF *MODUS OPERANDI*

Letter ("email") from a colleague in China:

"Would like to 'work in my lab' but hesitant because of the 'strangeness' of my work [as medical geneticist]… and what

does a Julia Creek Dunnart have to do

with anything?"

STRANGENESS OF *MODUS OPERANDI*

- Living Pro-, Meta -, Eutheria Plants, Fungi (eukaryotes), Bacteria, and Archaea (pro-karyotes) ALL descended from LUCA!

“STRANGENESS” & THE PRACTICE OF MEDICAL GENETICS

Practicing medicine, pediatrics, medical genetics, and developmental pathology from the perspective of a

ZOOLOGIST

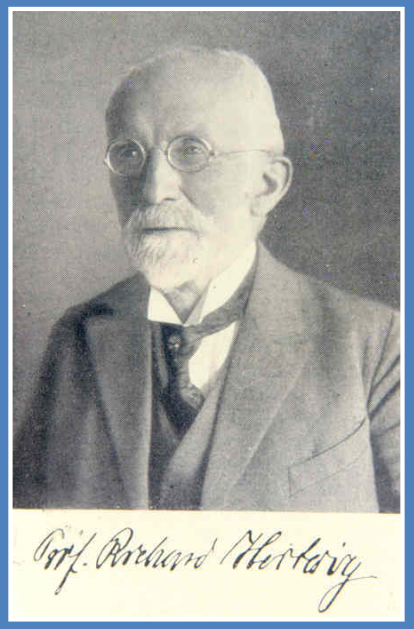
(JMO, BA ZOOLOGY; 1956)

specifically, as a MEDICAL MORPHOLOGIST

AS A ZOOLOGIST

Trained in comparative vertebrate embryology (1954), evolution, basic genetics, and the biological basis of sex determination and sex differentiation by Emil Witschi, University of Iowa, Iowa City

Emil Witschi
1964, Madison, WI



Richard Hertwig
in his old age

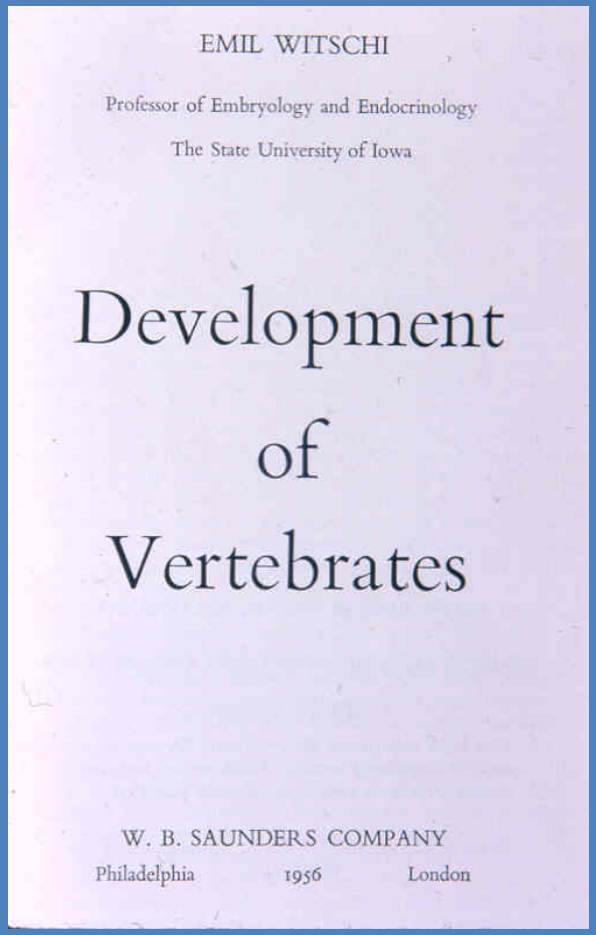
AS A ZOOLOGIST

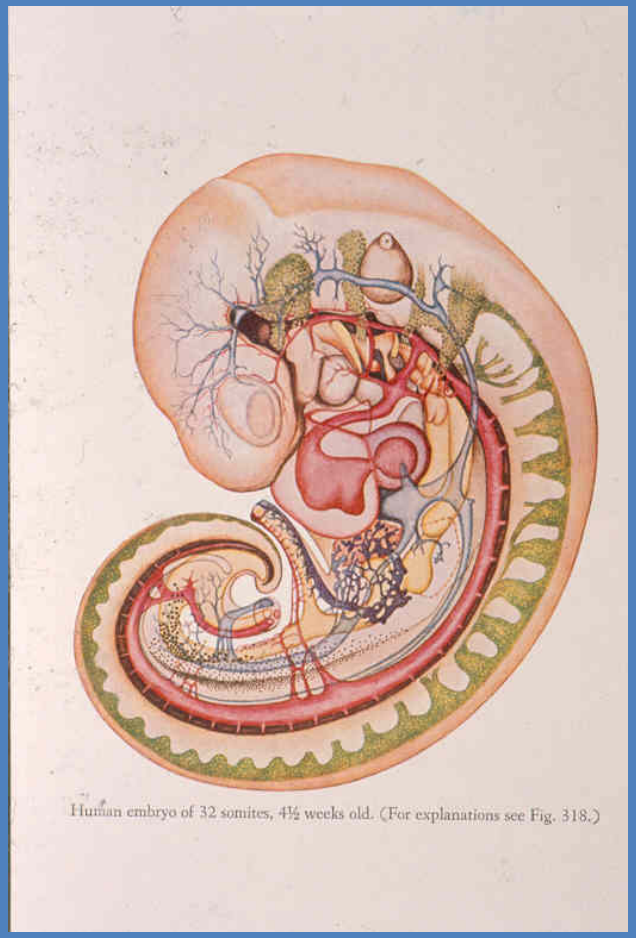
"Ontogeny recapitulates phylogeny" (1874)

Cellular Pathology

Müllerian ducts
Smooth shark of Aristotle

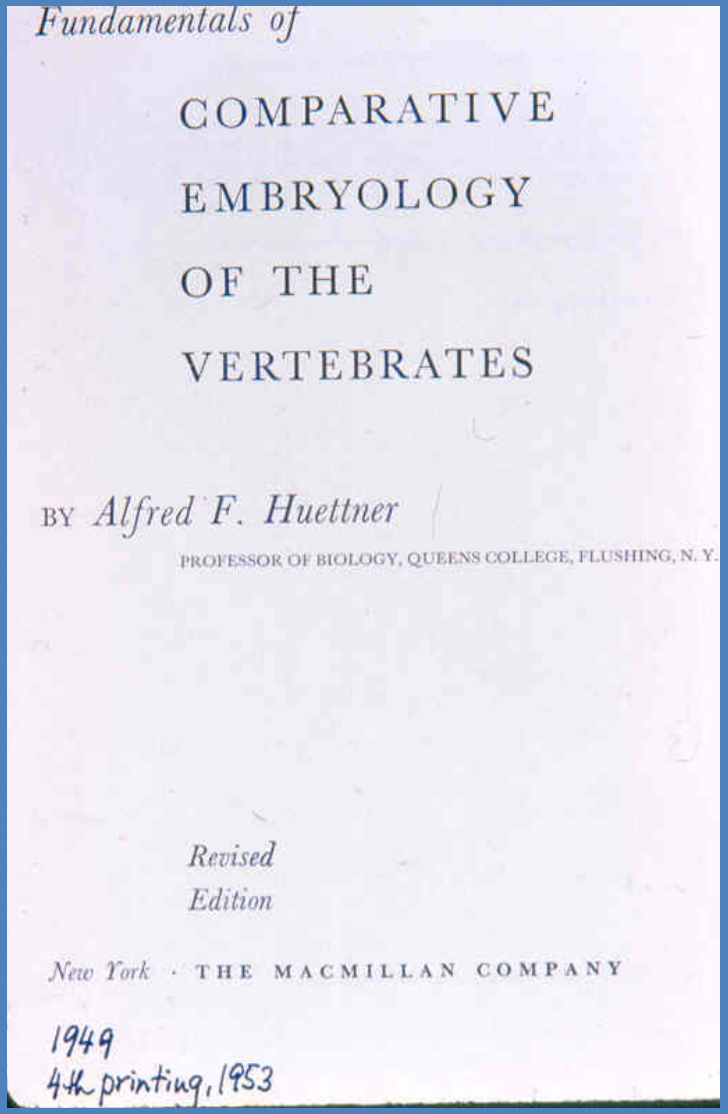
WITSCHI, 1956





Witschi's embryology book not published until 1956, instead in 1954 he assigned A.F. Huettner:
Fundamentals of Comparative Embryology of the Vertebrates

HUETTNER


Fundamentals of

COMPARATIVE
EMBRYOLOGY
OF THE
VERTEBRATES

BY *Alfred F. Huettner*

PROFESSOR OF BIOLOGY, QUEENS COLLEGE, FLUSHING, N. Y.

Revised
Edition

New York · THE MACMILLAN COMPANY

1949
4th printing, 1953

"This organizer is now better known as the chorda-mesodermal field which is the first or primary field to exist in the amphibian germ. Secondarily it gives rise to secondary organizers or subordinated fields, such as nose, eye, gill and others."

AS A ZOOLOGIST

DIE INTERSEXUALITÄT
Claus Overzier


DIE
INTERSEXUALITÄT

HERAUSGEGEBEN VON

PROF. DR. CLAUS OVERZIER

Oberarzt der Medizinischen Universitäts-Klinik Mainz

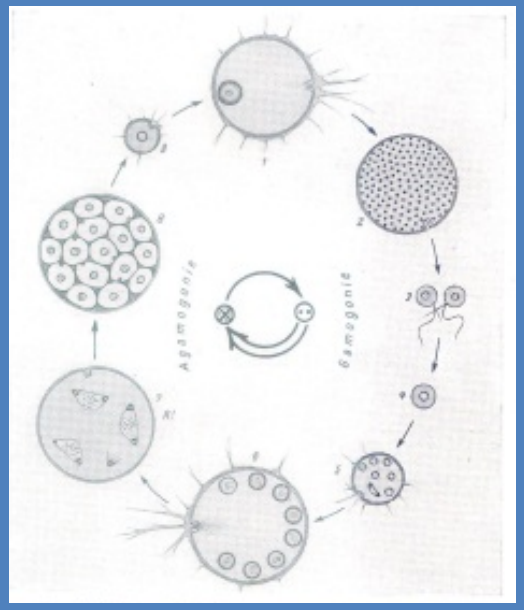
UNTER MITARBEIT VON

M. L. Barr, London/Canada · J. R. Bierich, Hamburg · W. M. Davidson, London/Engl. C. E. Ford, Harwell/England · H. Grüneberg, Göttingen · R. Hasche-Klünder, Hannover G. A. Harrer, Basel/Schweiz · H. D. Hermann, Köln-Lindenthal · K. Hoffmann, Mainz W. Koch, München · B. Lennox, Glasgow/Schottland · J. M. Opitz, Iowa City/Iowa, USA C. Overzier, Mainz · J. H. Schulte, Berlin-Charlottenburg · D. R. Smith, Reading/England M. Watzka, Mainz · E. Witschi, Iowa City/Iowa/USA · J. Zander, Köln-Lindenthal

Mit 193 Abbildungen in 447 Einzeldarstellungen
und 38 Tabellen

19 61

GEORG THIEME VERLAG · STUTTGART



Gundlagen der Intersexualität
Witschi & Opitz
Written in 1959

SINCE 1959

Introduction of the developmental field concept (DFC) into medical morphology

Primary malformations explained as DF defects on the basis of:

- Heterogeneity
- Homology
- Phylogeneity

HETEROGENEITY

Different causes leading to ***identical*** (primary) malformations identifying ***specific dys****morphogenetic units* of the embryo which must also be specific developmental field equivalents under ***normal*** circumstances.

HOMOLOGY

"Die ursprünglichen Bildungsfehler sind nicht wider die Natur"

Primary malformations [in humans] are not contrary to nature…, especially since so many are the ***normal*** state in more or less closely related species (***Atavisms***, 1839).

J.F. Meckel, 1812,

Hdb. path. Anat.

HOMOLOGY

Homology of structure infers homologous morphogenesis by virtue of descent, with modification, from a common ancestor with prototypic pattern of development involving *identical signal transduction paths* (q.v. Darwin 1859, von Baer 1828, Gilbert SF, 2010)

HOMOLOGY

"FACILE COSA È FARSI UNIVERSALE…"

"…it is easy to become universal, since all land animals resemble each other in the parts of their body, that is, muscles, nerves and bones, and differ only in length and size"

Leonardo da Vinci

(Capra F. 2007: The science of Leonardo, p 34)

"…proper phylogenetic analysis should only be based on homology" (Fitch, Trends Genet, 2000)

PHYLOGENEITY

Corrolary of ***homology***: If ≥ 2 different species can develop an "identical" malformation (e.g. HPE), then they share corresponding developmental field structure and developmental field dynamics by virtue of descent…

FIELDS AND MODULES

Developmental fields are the self-organizing units of morphogenesis; and that if permanent evolutionary change of structure involves changes of developmental field dynamics, then, the units of development (fields) are identical to the units of evolution (modules).

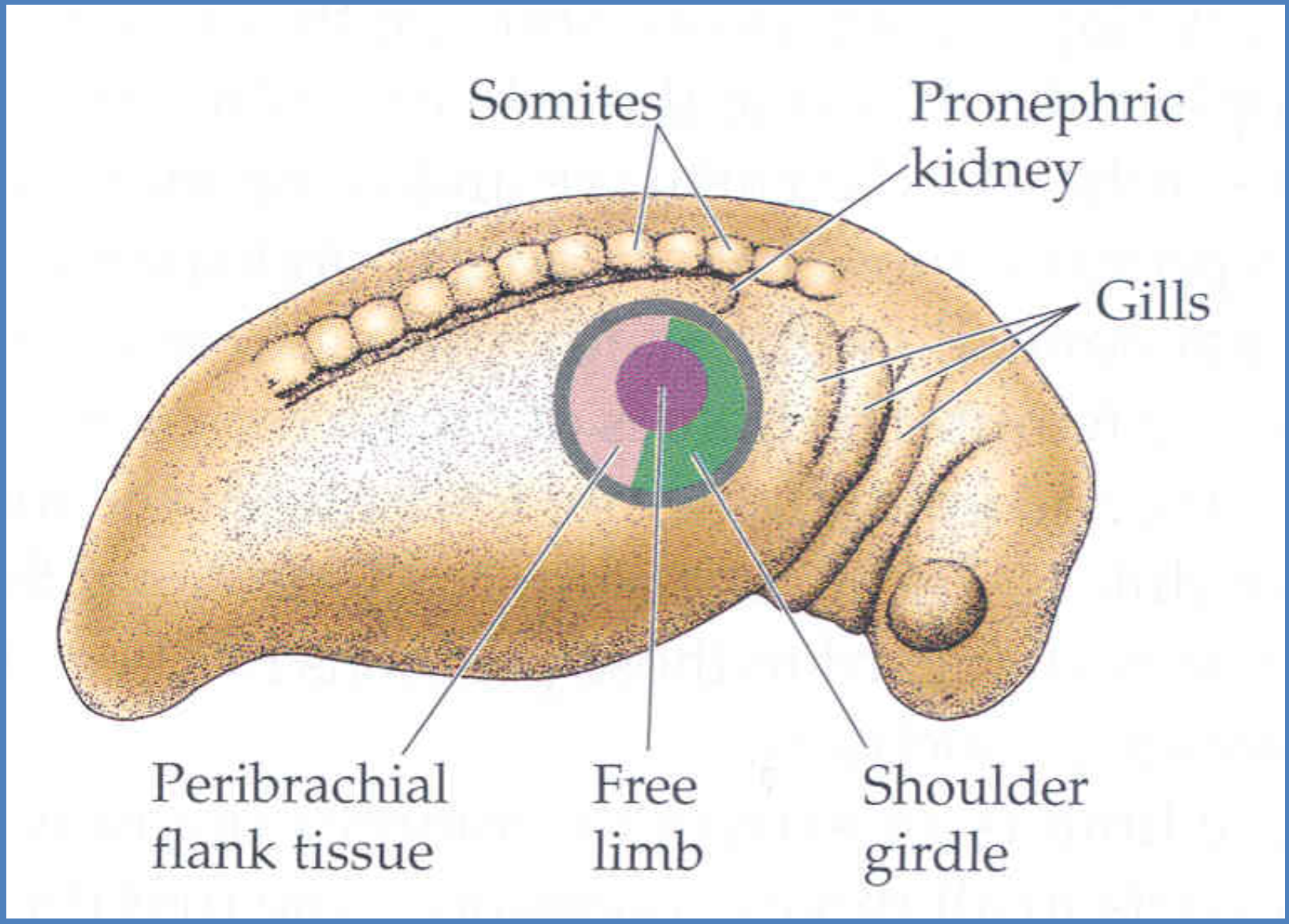
(q.v. Schlosser, Wagner, Modularity in Development and Evolution, 2004)

FIELD DYNAMICS

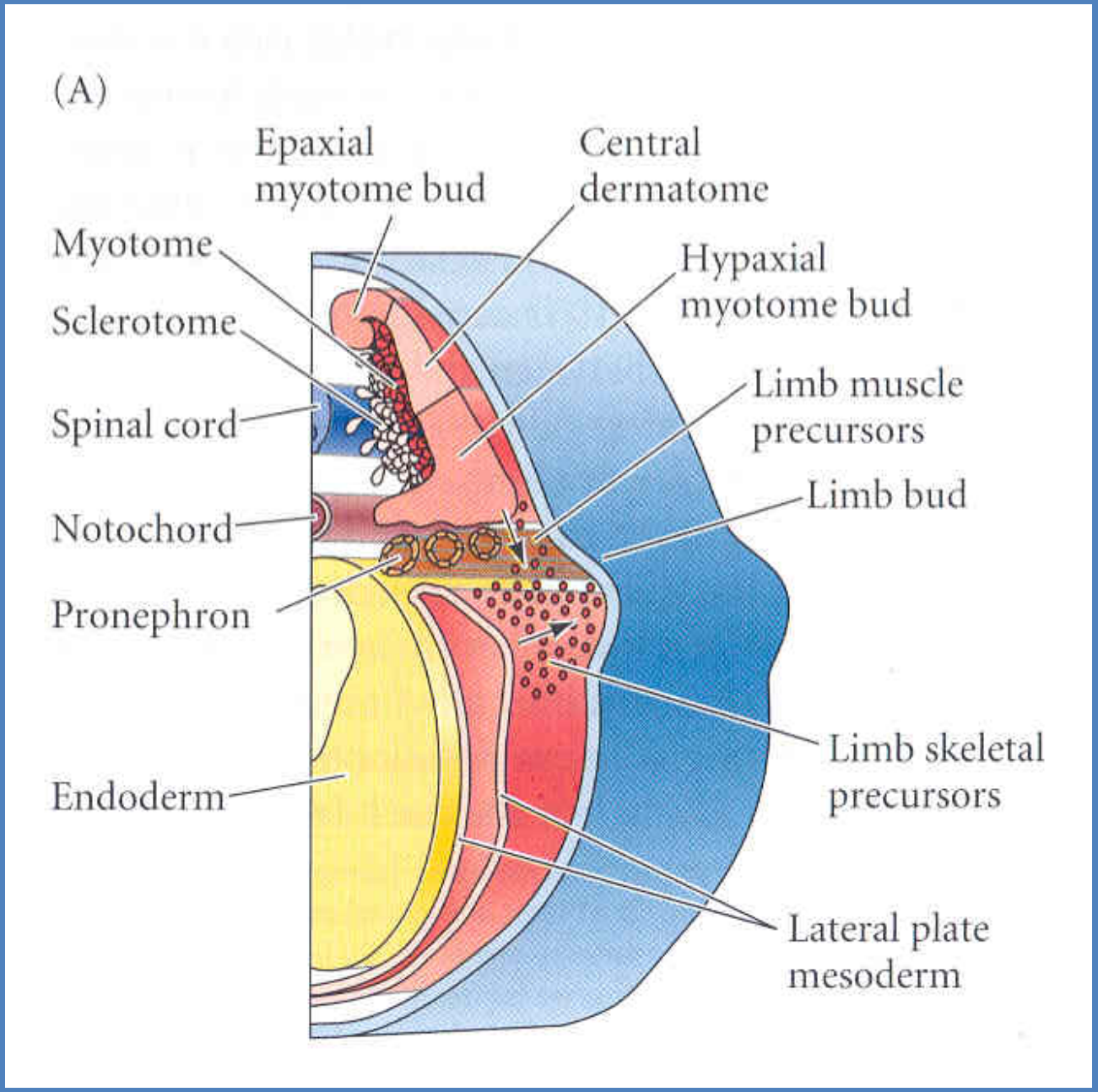
Embryonic progression (hierarchical)

- *Primary field* (Spemann & Mangold, 1924; Spemann, 1936)

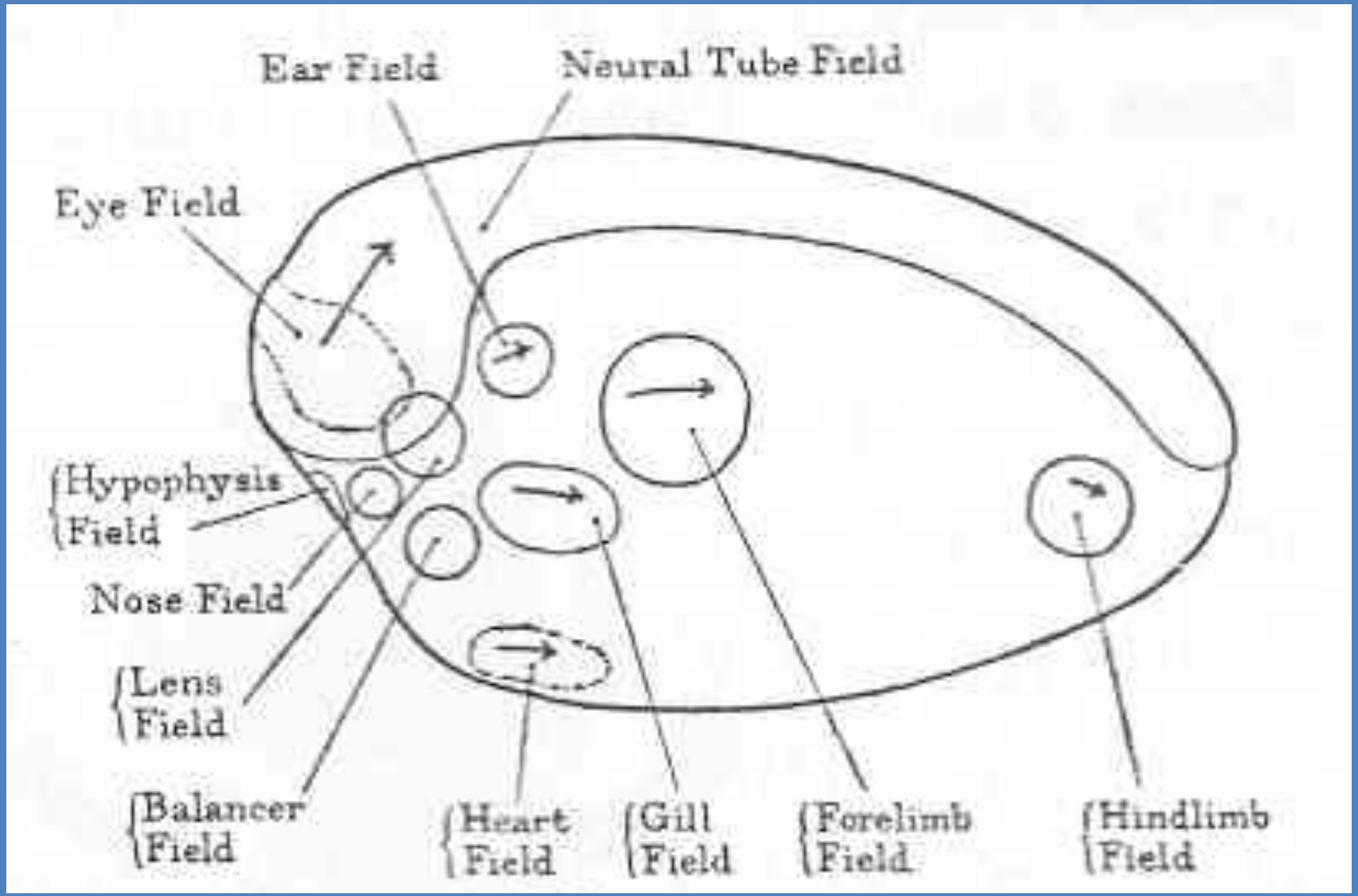
- *Progenitor fields* (Davidson, 1993): "…spatially disposed cellular elements from which a structure originates…syn. *Anlage*"; upstream molecular expression domains specifying structure. Have definite boundaries.



Gilbert, Fig. 13.2, 2010

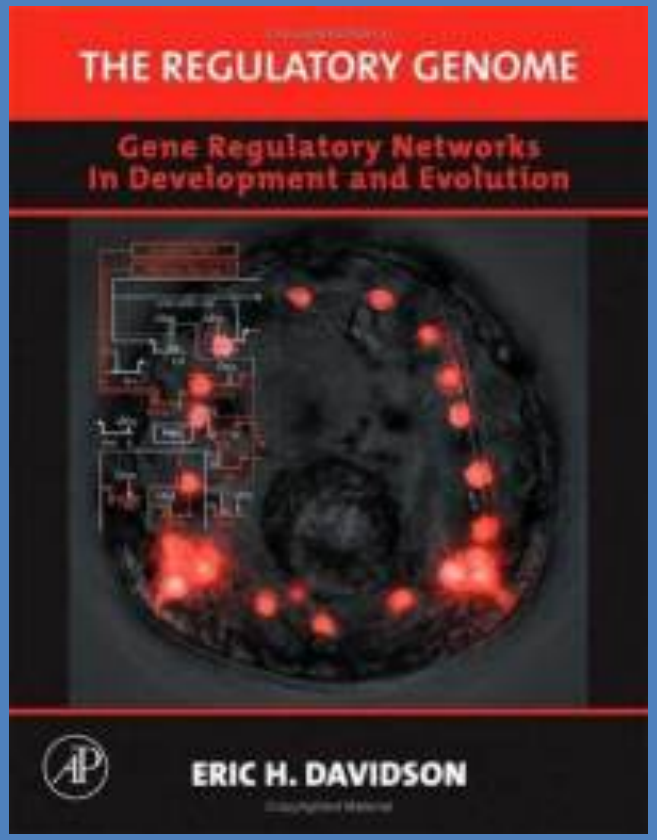


Gilbert, Fig. 13.3, 2010



Huxley and DeBeer 1934

FIELD DYNAMICS



- *Secondary* ("epimorphic") *fields* are the morphogenetic units of the embryo in which final morphogenesis occurs and which remain fields as long as (mutant) gene or teratogen can alter final structure.

  (q.v. Davidson EH. The Regulatory Genome, 2006)

DEVELOPMENTAL FIELDS

Nobel Prize, 1935

Spemann & Mangold, 1924

Primary organizer ("field")

"Induktion ist nichts anderes als Feldwirkung":

Induction is nothing else than field effect.

FIELD DYNAMICS

Processes in developmental fields are:

- Epigenetically complex, non-linear, reciprocally interactive,
- Spatially coordinated and ordered,
- Temporally synchronized,
- Phylogenetically highly constrained (many genes, few structures; many mutations, few anomalies) into few final developmental paths.

FIELD DYNAMICS

And if a specific ***teratogen*** (e.g. FAS, jervine, cyclopamine) leads to a malformation (e.g. HPE) morphogenetically identical to one of ***genetic*** origin (e.g. *SHH* mutation), then it must have interfered with the same basic signal transduction pathway (e.g. cholesterol modification of the sonic hedgehog protein).

CREDO OF AN UNREGENERATE GENETIC MORPHOLOGIST

- Everything that develops has evolved;
- Everything that occurs during embryogenesis, whether normal or ***primary malformation***, has been made possible by evolution;
- Therefore, ***secondary anomalies*** are those not enabled by evolution (e.g. ADAM sequence with amputations, pseudosyndactyly, placenta adherent to brain, short cord…)

ONTOGENY VS. PHYLOGENY

During ***ontogeny*** of direct-developing organisms morphogenesis precedes histogenesis, (i.e. the establishment of cell linages)

- Meckel *"…dass die Form vor der Textur entsteht"*;
- Hence, malformed organs are usually histologically normal, and most cancers are defects of cell lineages, not of organs

ONTOGENY VS. PHYLOGENY

Phylogeny histogenesis precedes morphogenesis (E.H. Davidson), e.g.

- Photoreceptors before eye
- Contractile cells before heart…

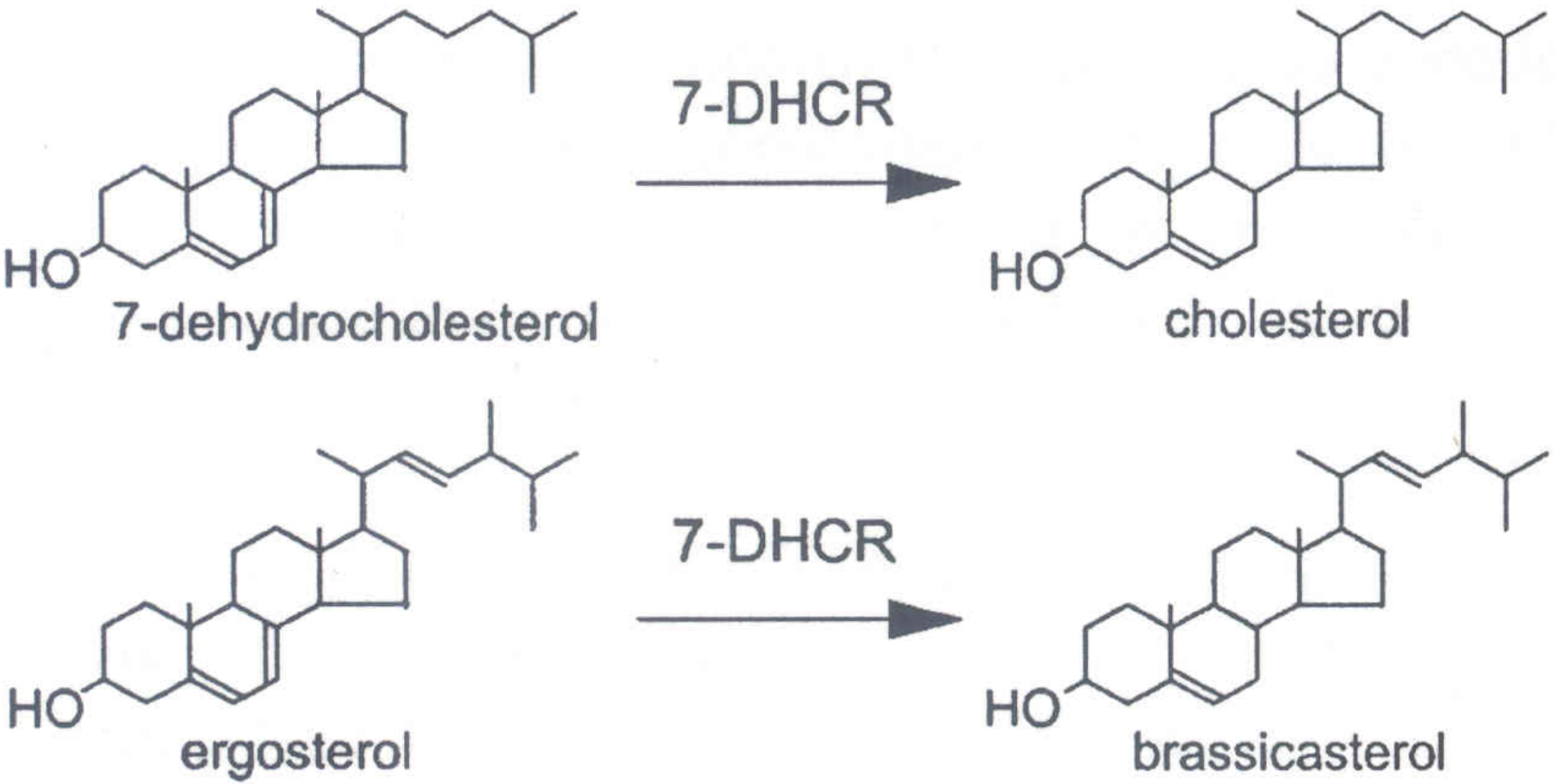
Thus, we are enabled to…

THE DELIGHTS OF CLINICAL PALAEONTOLOGY

e.g. 1.) *DHCR7* activity present in plants and animals, therefore in LUCA?...No!

Because: Biosynthesis of cholesterol requires 11 atoms of 0_2, hence could not have occurred before the ***Great Oxygenation***, 2.4 – 2.2 billion years ago.

THE DELIGHTS OF CLINICAL PALAEONTOLOGY



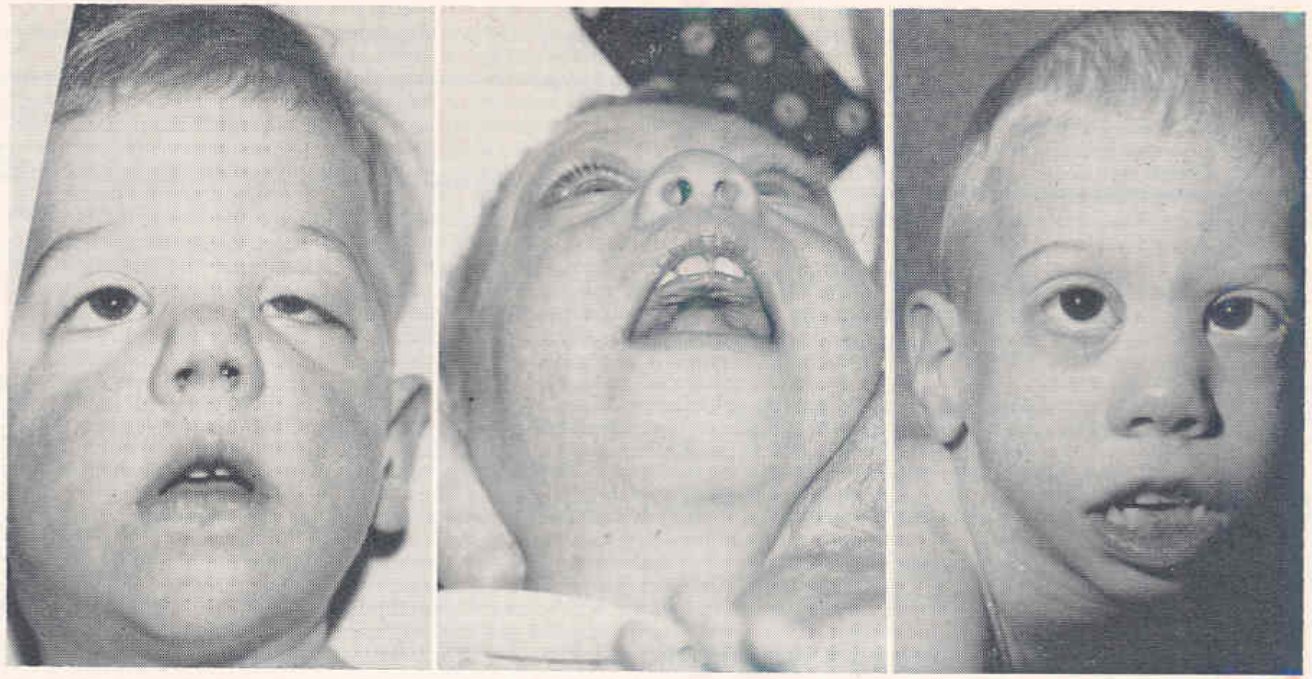


Fig. 3. From left to right: W. S., P. R., S. H. Note the broad alveolar ridge in patient P. R.

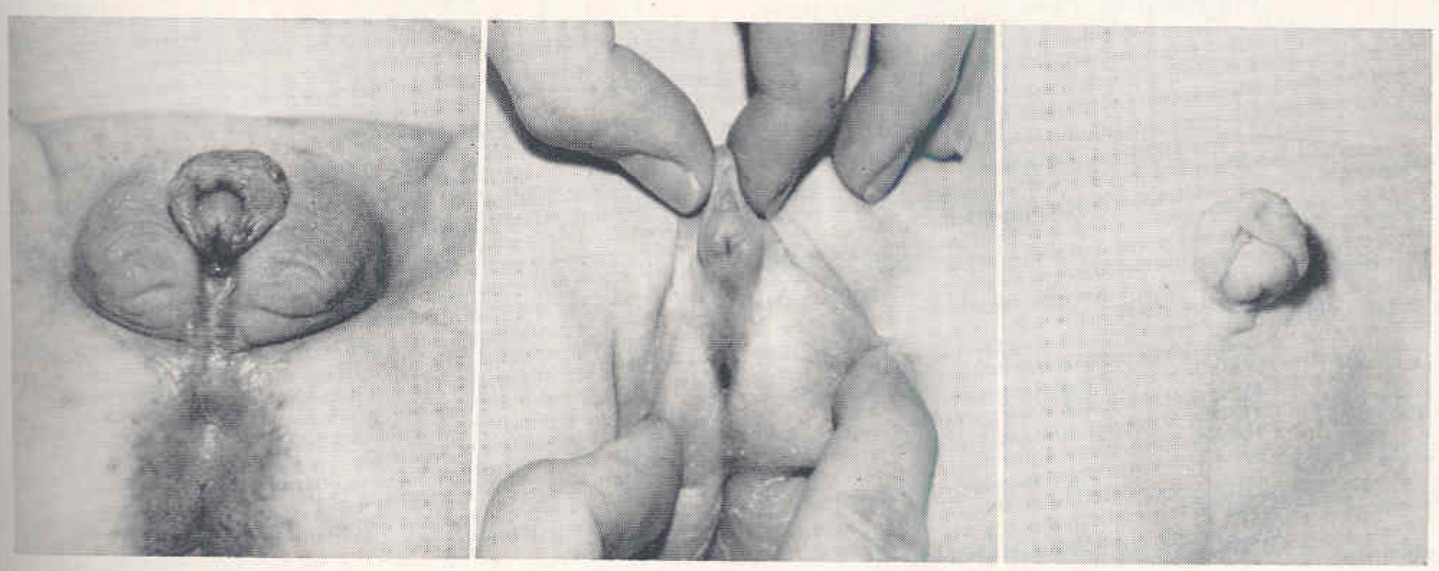
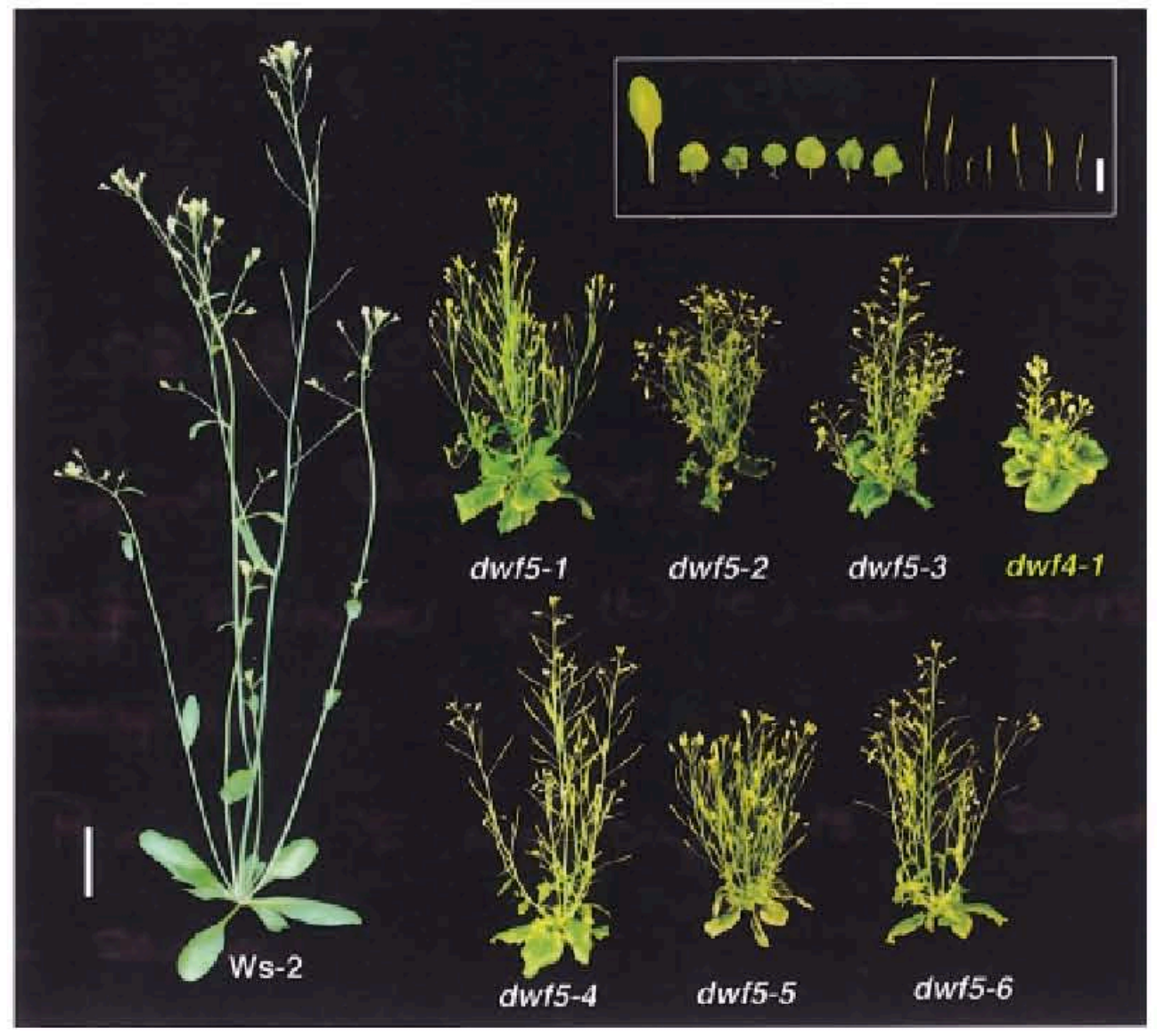


Fig. 4. From left to right: The genitals of patients W. S., P. R., and S. H.

COMMON ANCESTRY



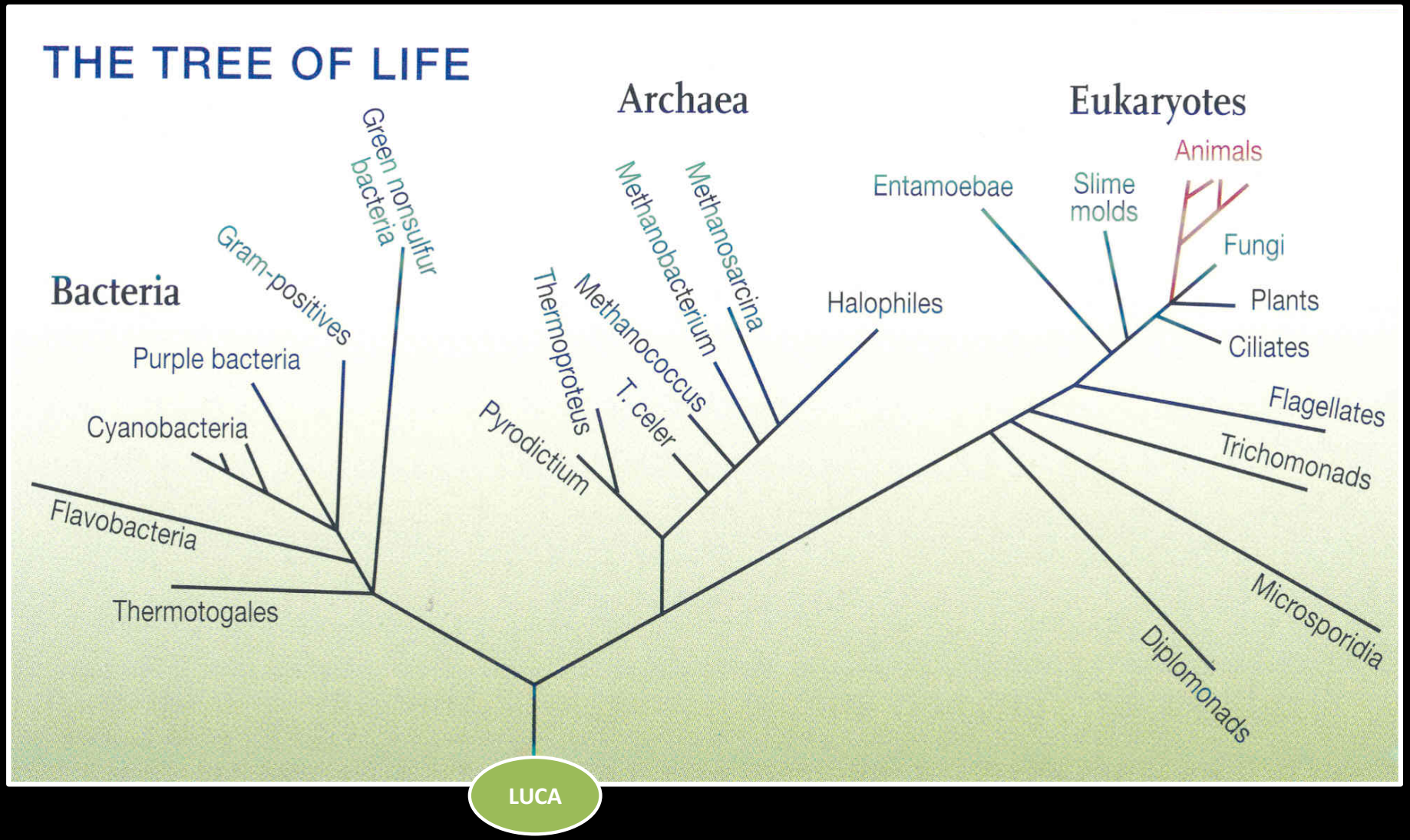
Note: Dwarfing phenotype; small, dark-green round leaves; short internodes and siliques; increased number of inflorescences.

THE DELIGHTS OF CLINICAL PALAEONTOLOGY

e.g. 2.) ***Perrault syndrome*** (type P): Due to mutation(s) of the ***HARS2*** gene coding for mitochondrial histidyl tRNA is highly conserved in eubacteria (*E. coli*), archaebacteria (*T. thermophilus*), fungi (*S. cerevisiae*), and other animals (*C.elegans*). Hence, must have been present in LUCA.

Pierce SB et al., PNAS, 2011

LUCA



Zimmer, 2001

LUCA

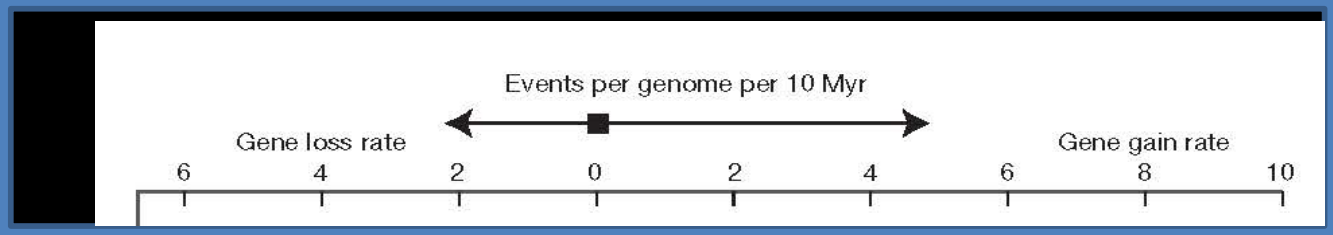
Antiquity of our genome

David & Alm, Nature 1/6/11: Phylogenomic method (AnGST): Analysis of history of 3983 gene families of the 3 domains of life:

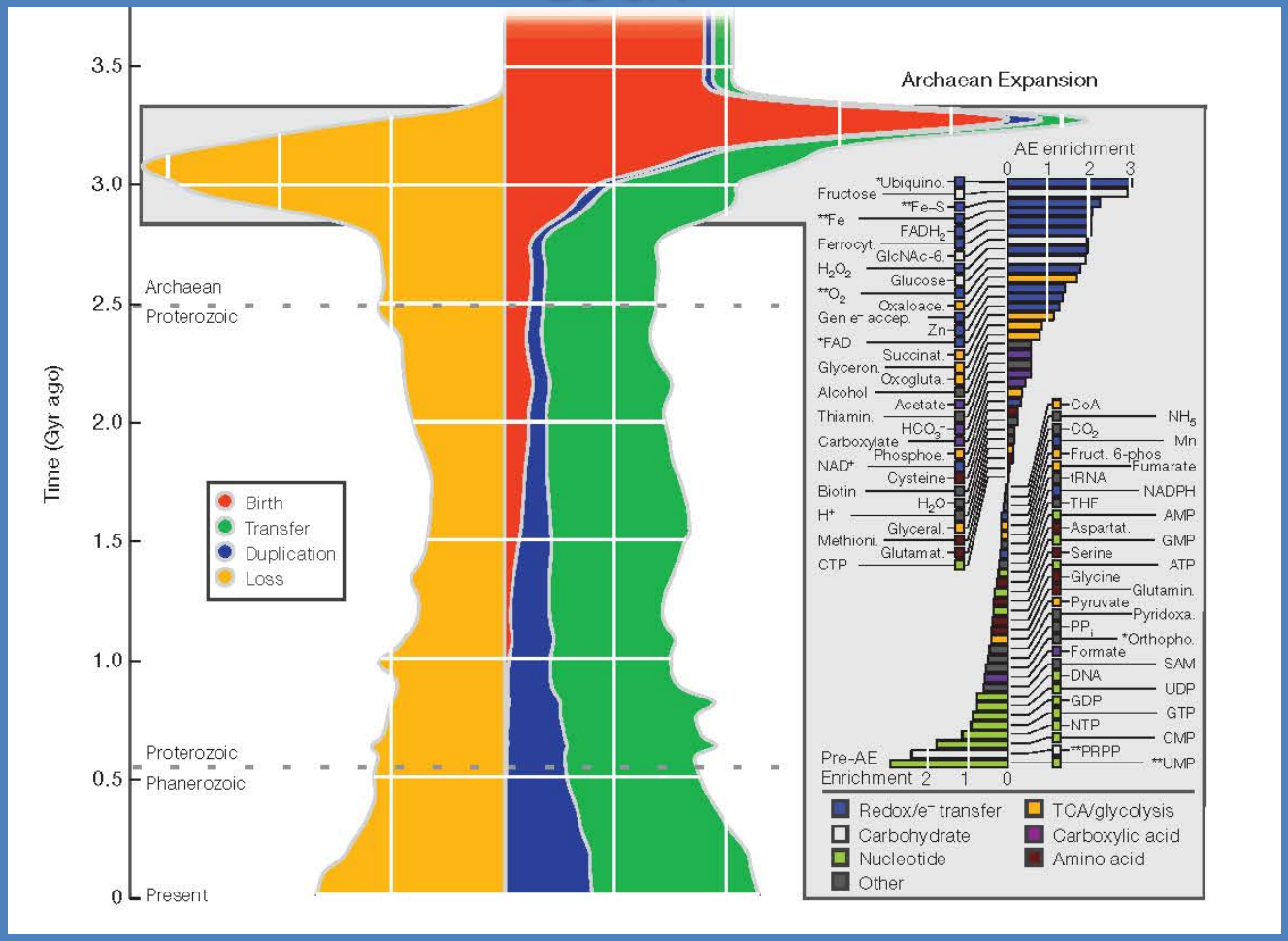
Showed that a brief period of Archaean expansion and rapid diversification of bacterial lineages 3.2 billions years ago, gave rise to 27% of all major modern gene families.

LUCA

Antiquity of our genome



LUCA



LUCA

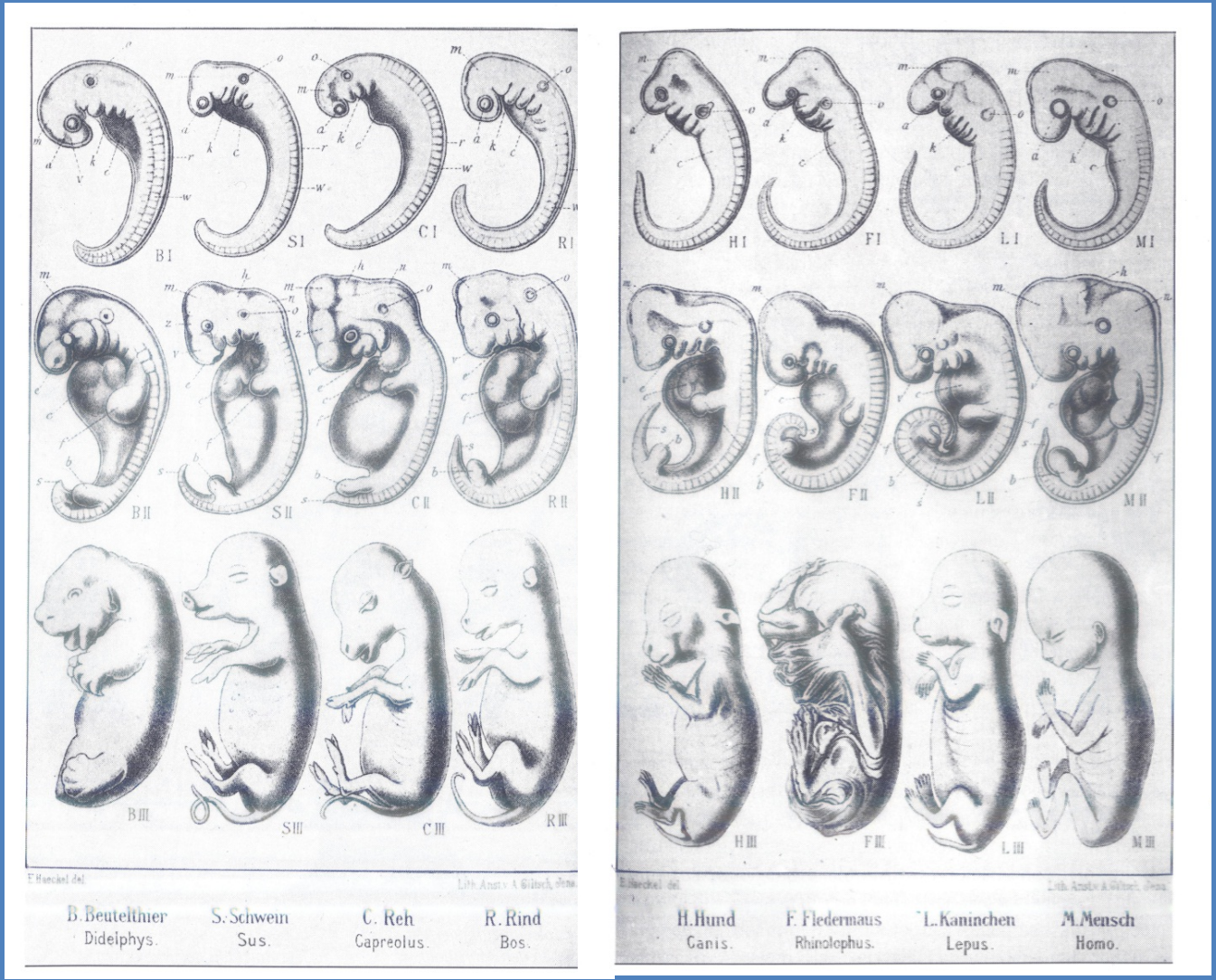
The “genomic hourglass”:

Haeckel: “Das biogenetische Grundgesetz”, i.e. [in some respects] ontogeny recapitulates phylogeny, now found to be correct (q.v. Kalinka et al., and Domazet-Lošo & Tautz, Nature, December 2010).

LUCA

The genomic hourglass in vertebrates:

Haeckel, 1905

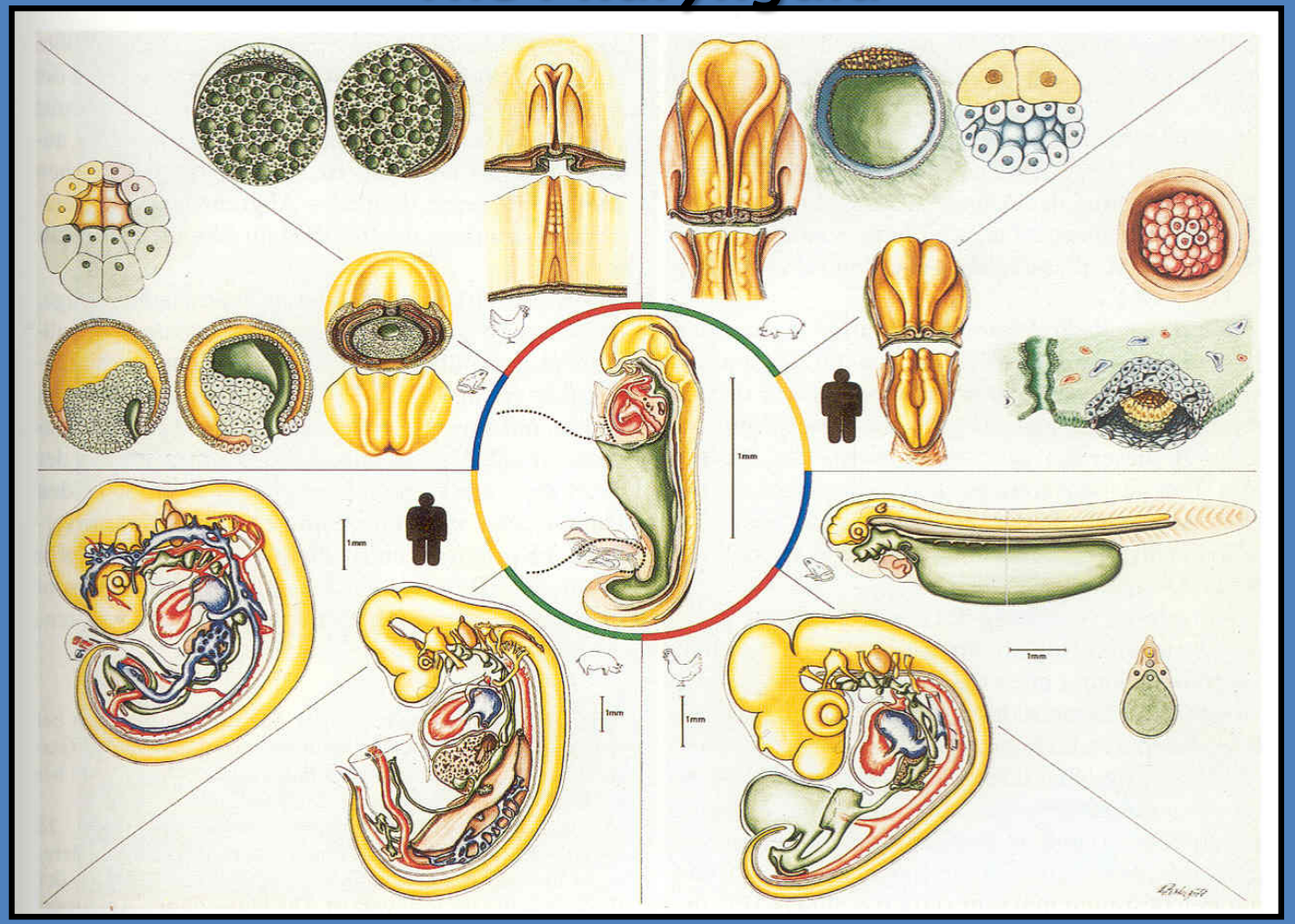


LUCA

The genomic hourglass in vertebrates:

Hinrichsen, 1990

The Pharyngula

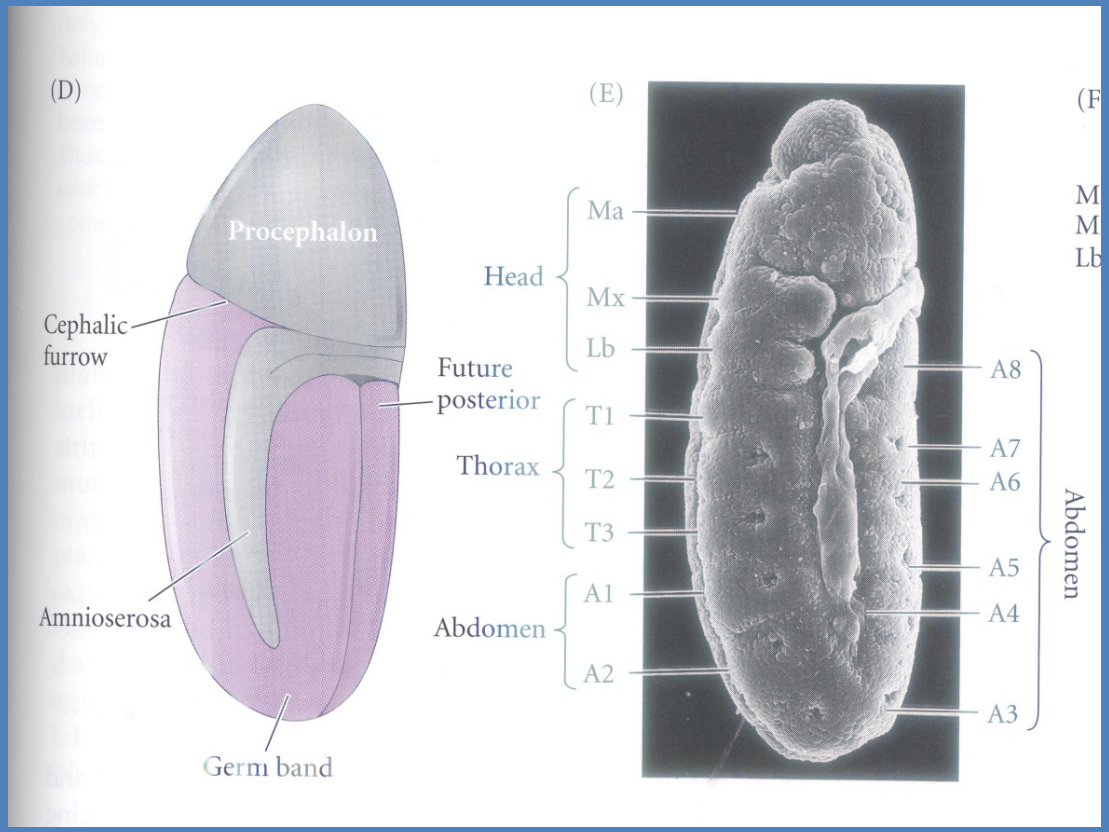


Duboule, 1994; Raff, 1996

(q.v. also the front cover of Raff, 1996)

LUCA

The genomic hourglass in insects*:



(*The “phylotypic” stage, Sander, 1983)

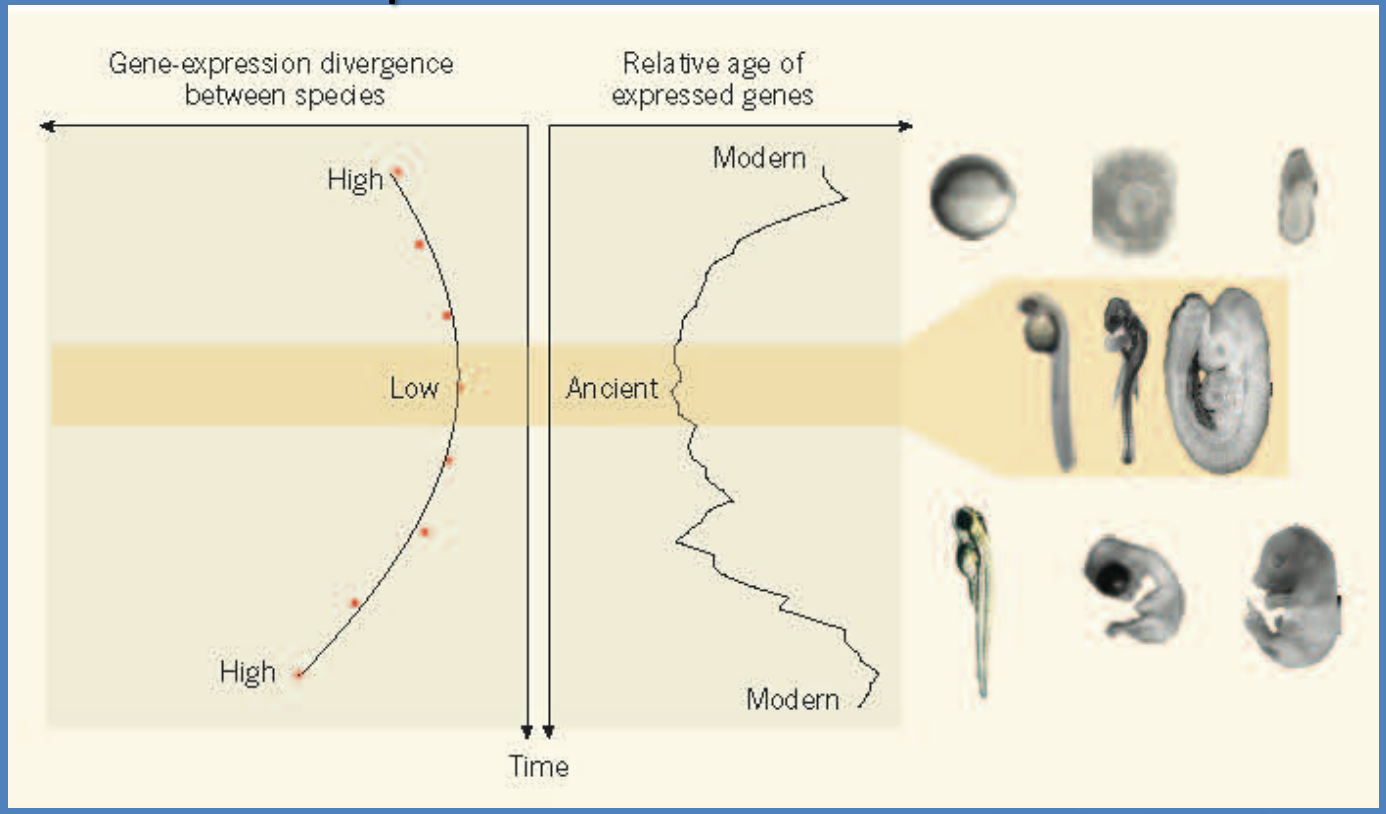
Fig. 2, Kalinka et al., 2010, based on 6 sequenced *Drosophila* species separated by up to 40 million years

LUCA

The genomic hourglass - Summary

The Phylotypic Stage

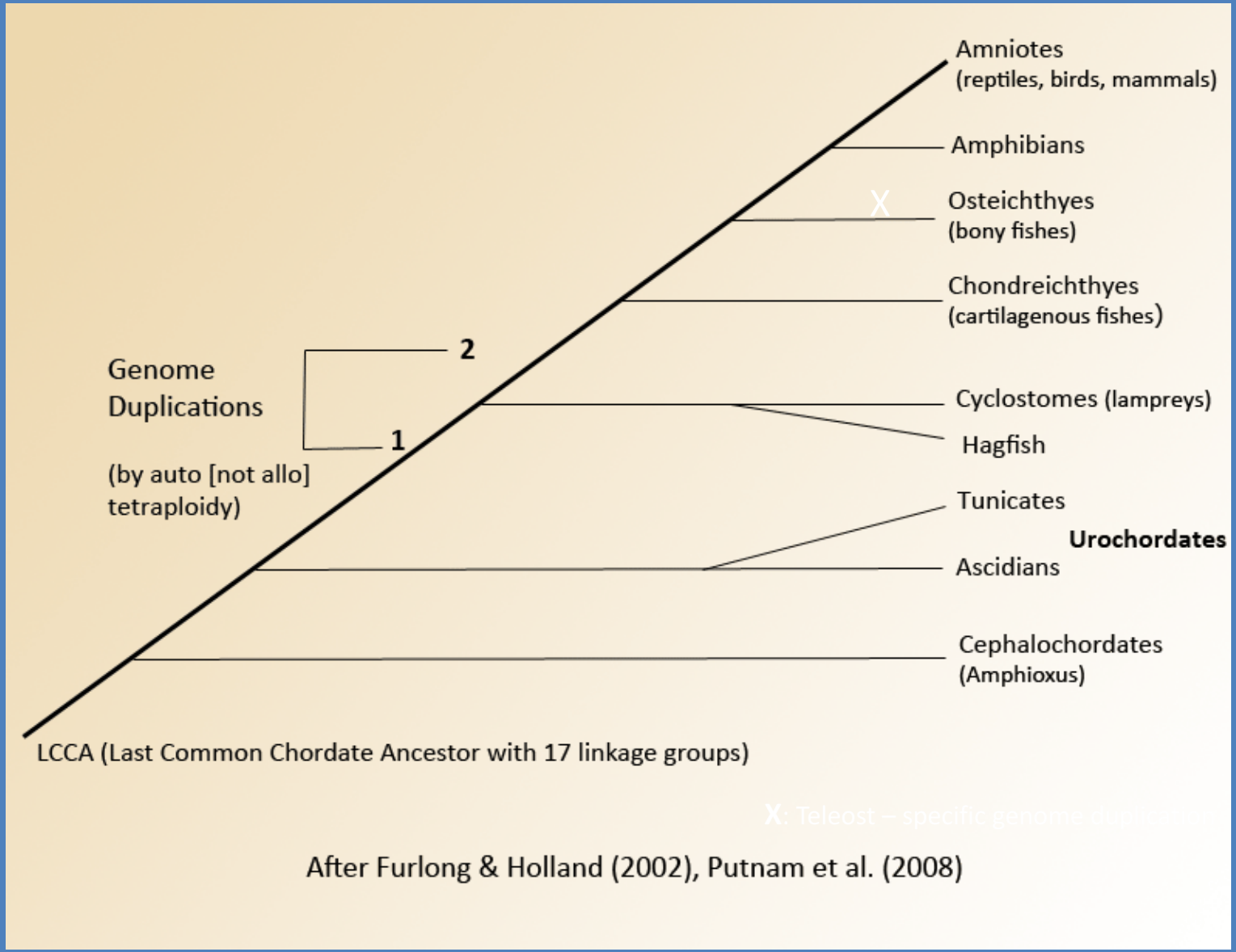
Drosophila Vertebrates



Prud'homme & Gompel,
Nature, December 2010

L > R: *D. rerio*
Chick
Mouse

OHNO (1970) CONFIRMED: TWO GENOME DUPLICATIONS



After Furlong & Holland (2002), Putnam et al. (2008)

THE LAST FRONTIER

(Seriously now, speaking as a member of a Division of Pediatric Pathology)

Fact: More fetuses die prenatally than are born alive

Fact: Many die because of genetic conditions, malformations, syndromes…

Fact: Most are not autopsied

Fact: In such cases appropriate genetic counseling is not provided/possible

Fact: In such "cases" (fetuses, infants) a huge amount of genetic pathology is yet to be discovered (our last frontier!)

THE LAST FRONTIER

Autopsy 11-028 (Permit restricted to chest only)

- 25-year-old primigravid woman with PCO, hypothyroidism, past CMV infection
- Oligohydramnios, IUGR, abnormal umbilical blood flow
- CS at 26 $^{4}/_{7}$ GA for “extreme IUGR”
- Transfer to Primary Children’s Medical Center for management, withdrawal of life-support at 53 weeks postconceptual age

THE LAST FRONTIER

Postnatal complications:

- Pneumothorax, umbilical, inguinal hernias
- Sepsis: *Candida, E. coli*
- Thrombocytopenia, osteopenia
- Adrenal insufficiency
- Retinopathy
- BPD

} of prematurity

- Severe PV leukomalacia
- Paralysis R. ½ diaphragm (plication)

AUTOPSY

- Small baby boy (46.5 vs. 61 cm; 3910 vs. 6000g) with characteristic facial appearance and skeletal findings (with fractures)
- Massive hepatosplenomegaly
- Relative micromelia
- EM of liver suggestive of a lysosomal disorder (Fibroblast culture failed)

DIAGNOSIS? RECURRENCE RISK?

Ref: Gilbert EF et al.*, Z Kinderhlk 114:259, 1973

*One of these co-authors present at the autopsy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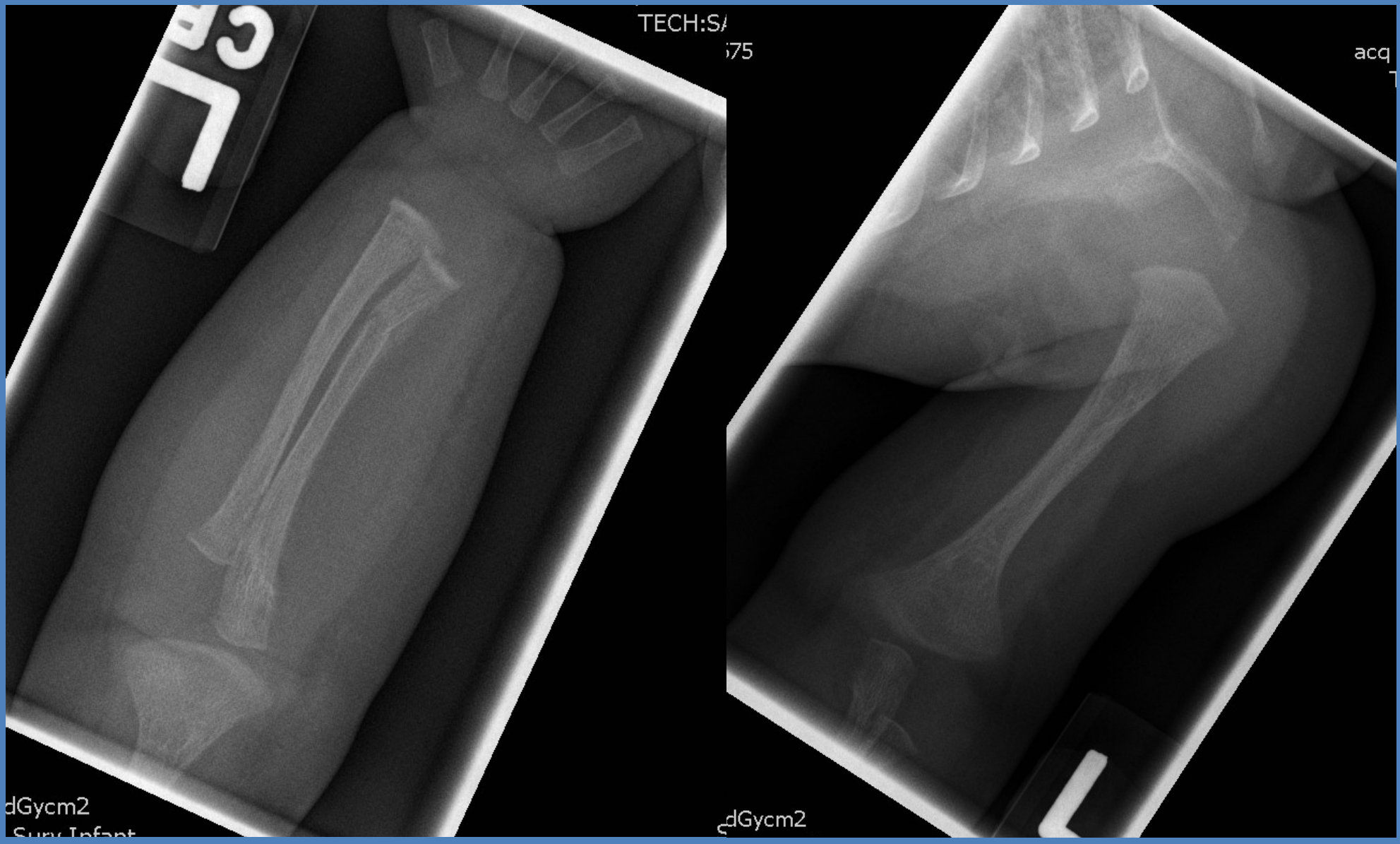
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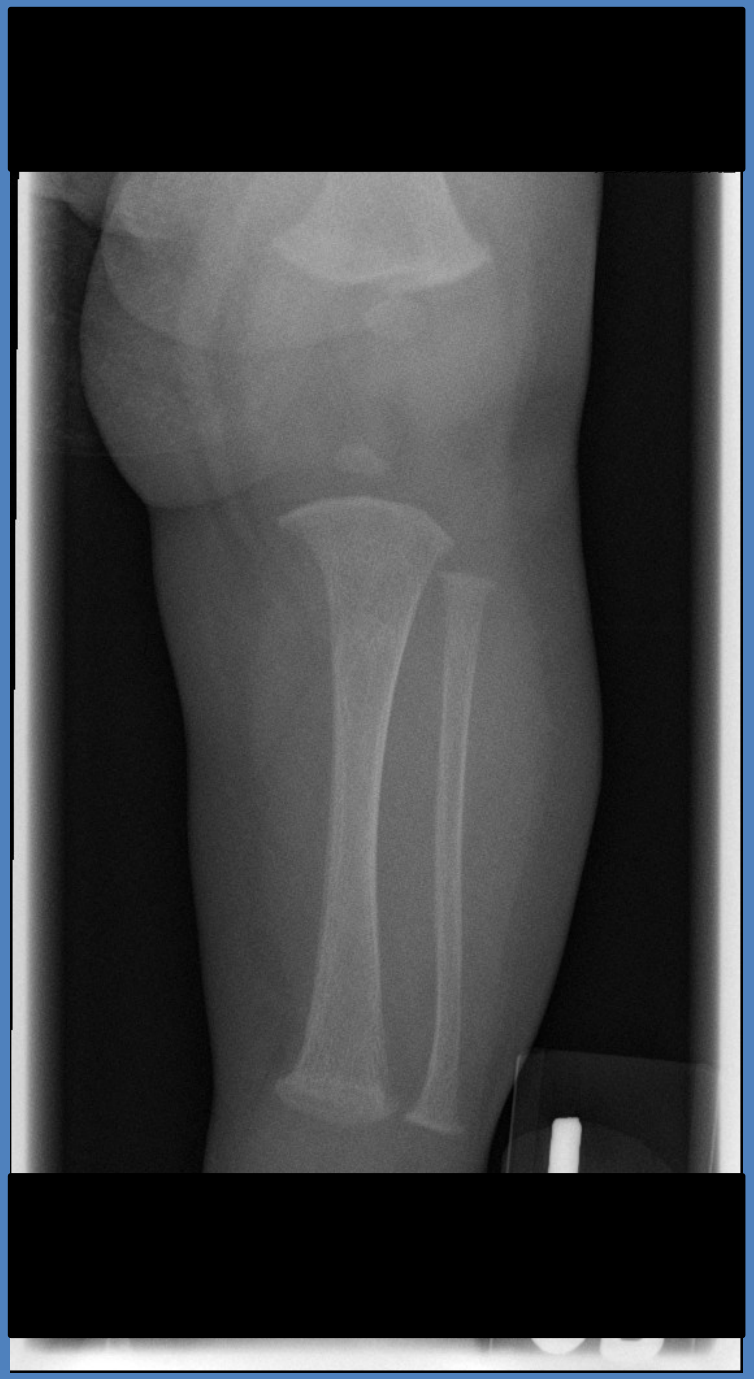


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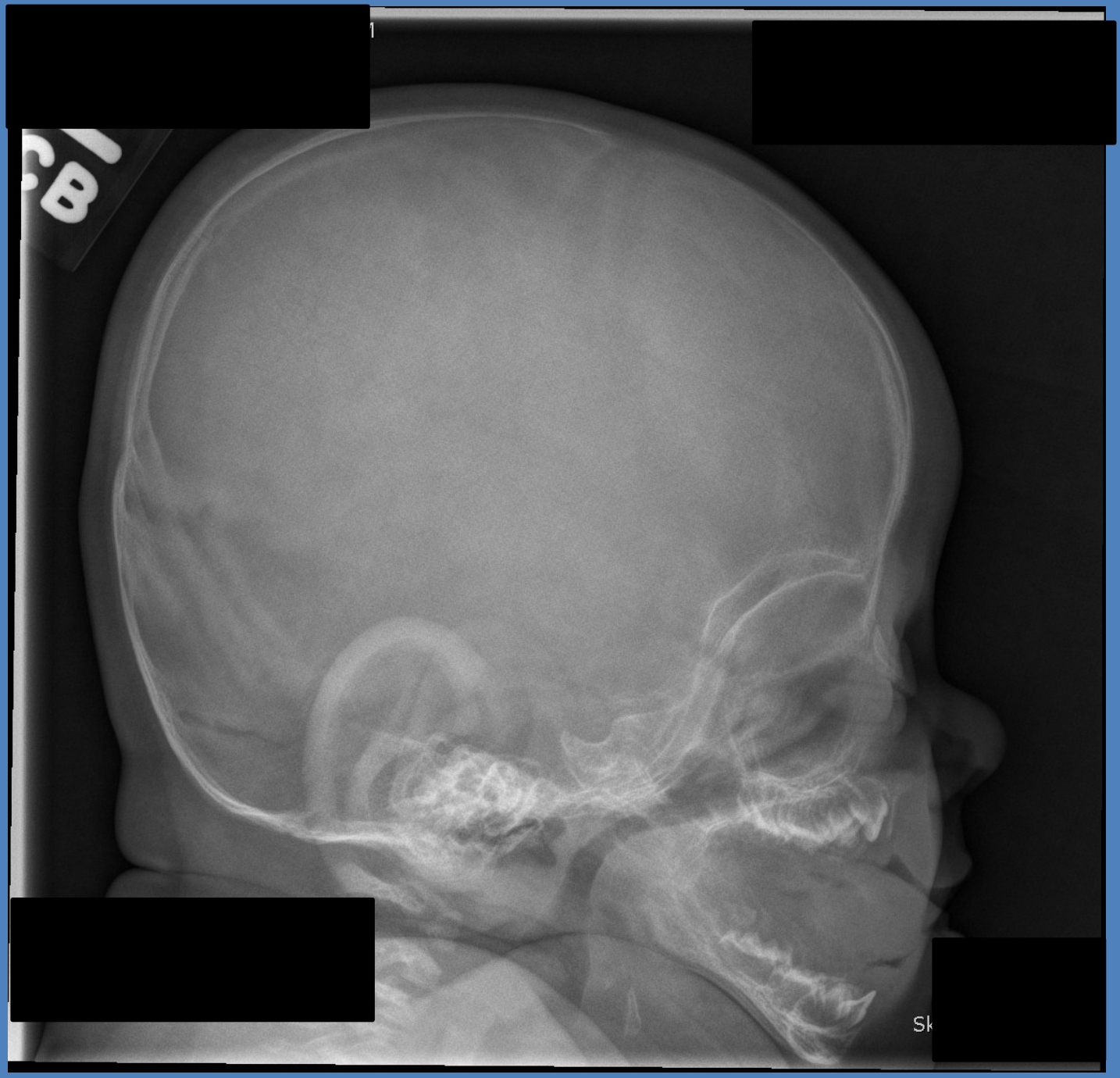


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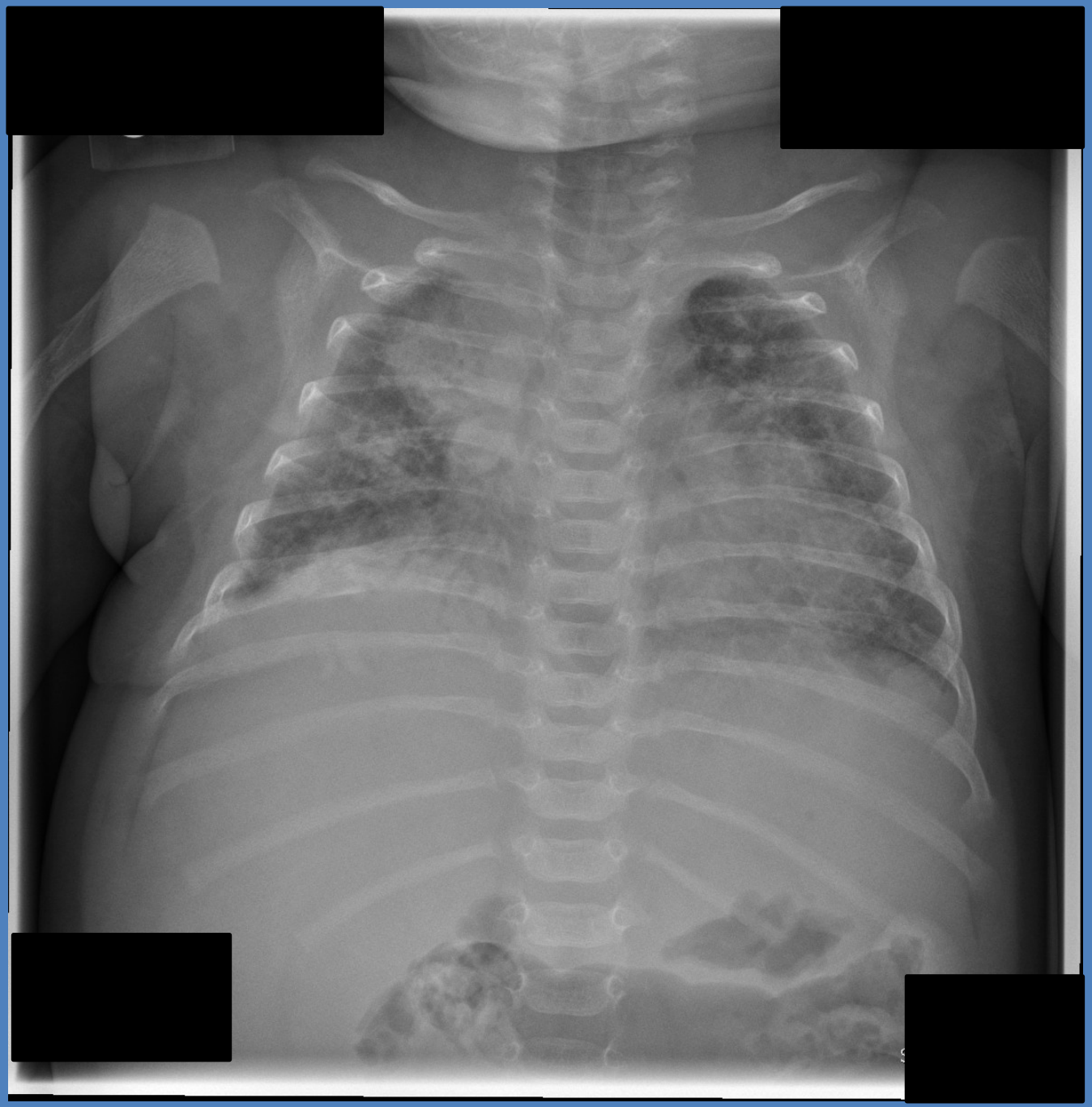
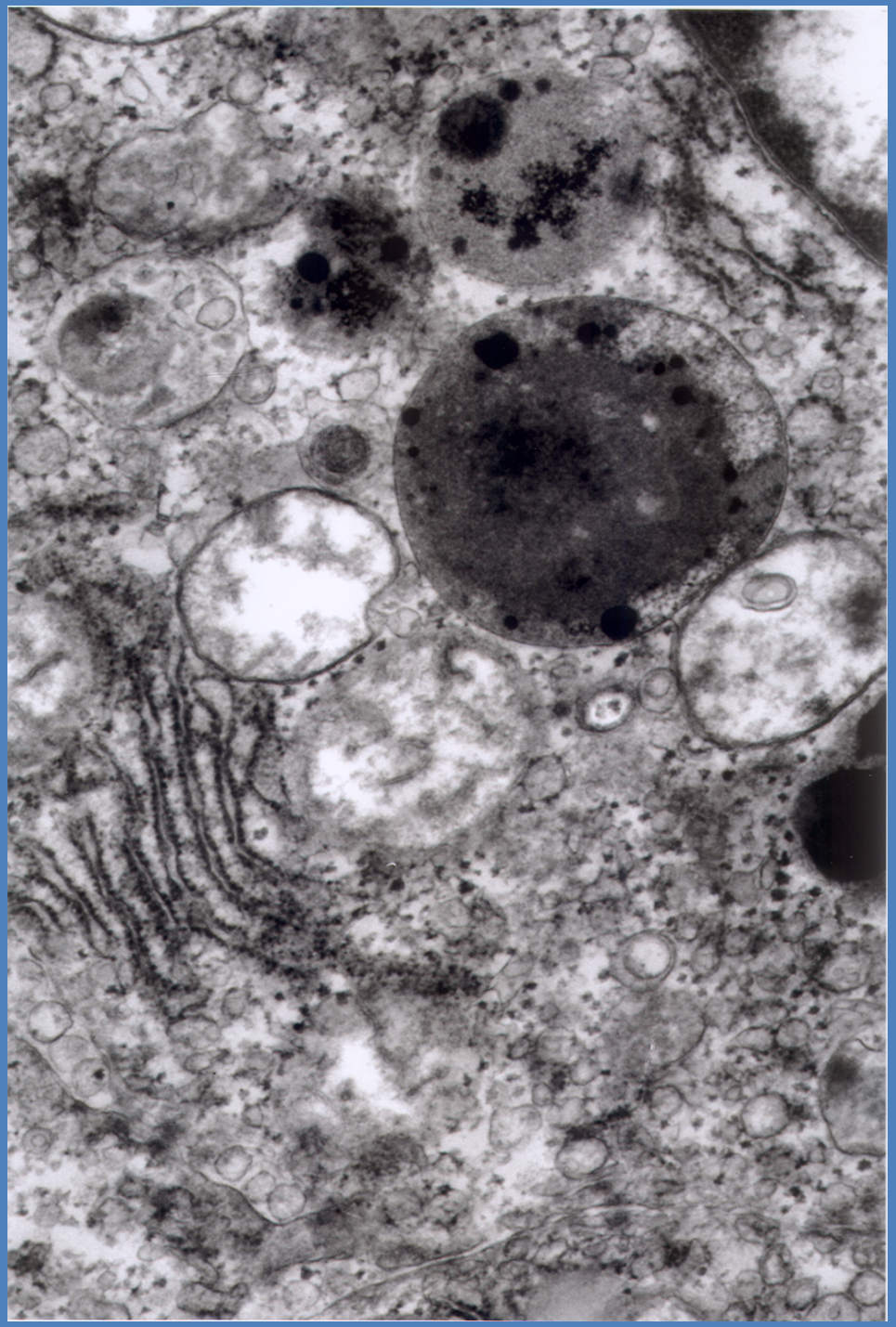
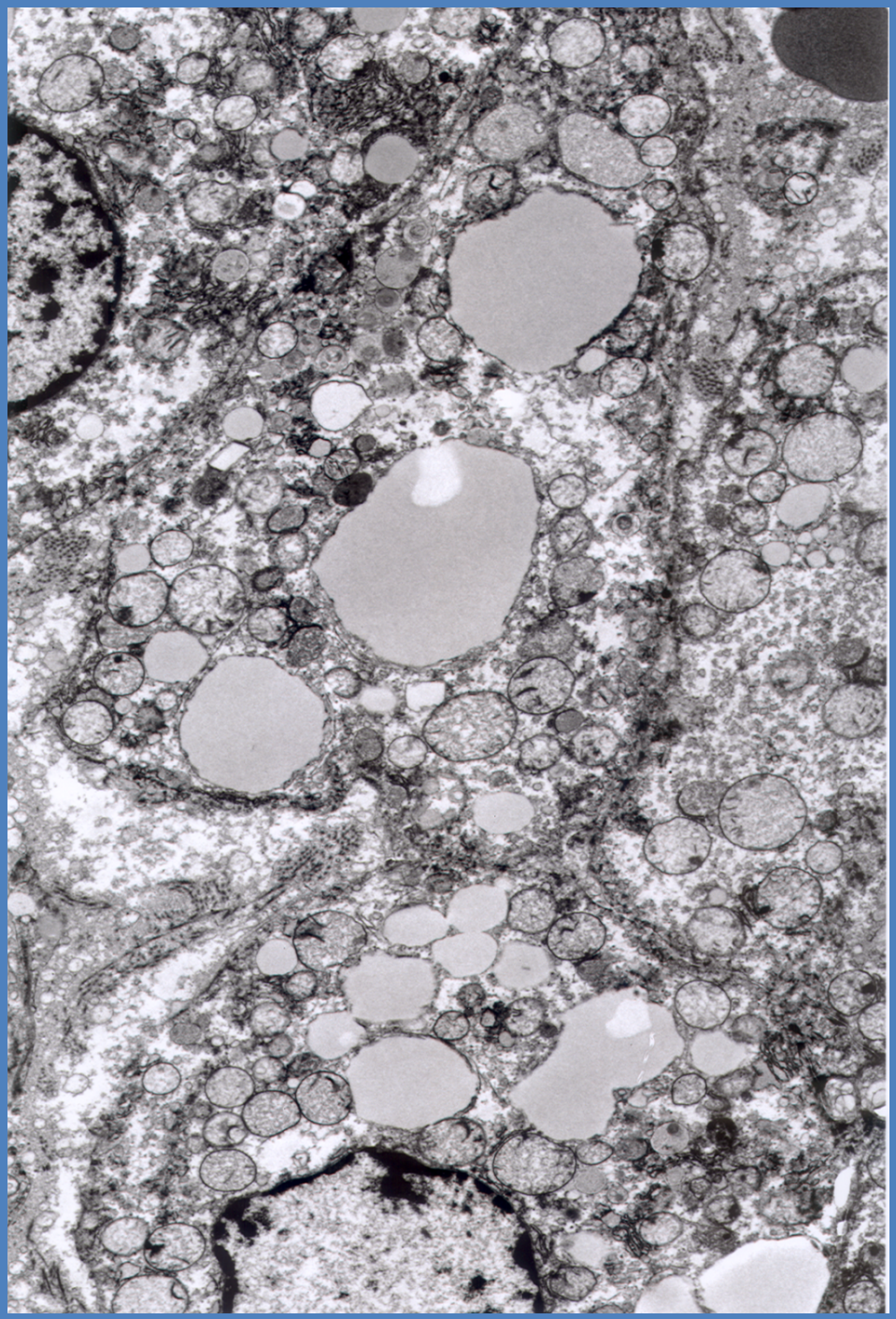
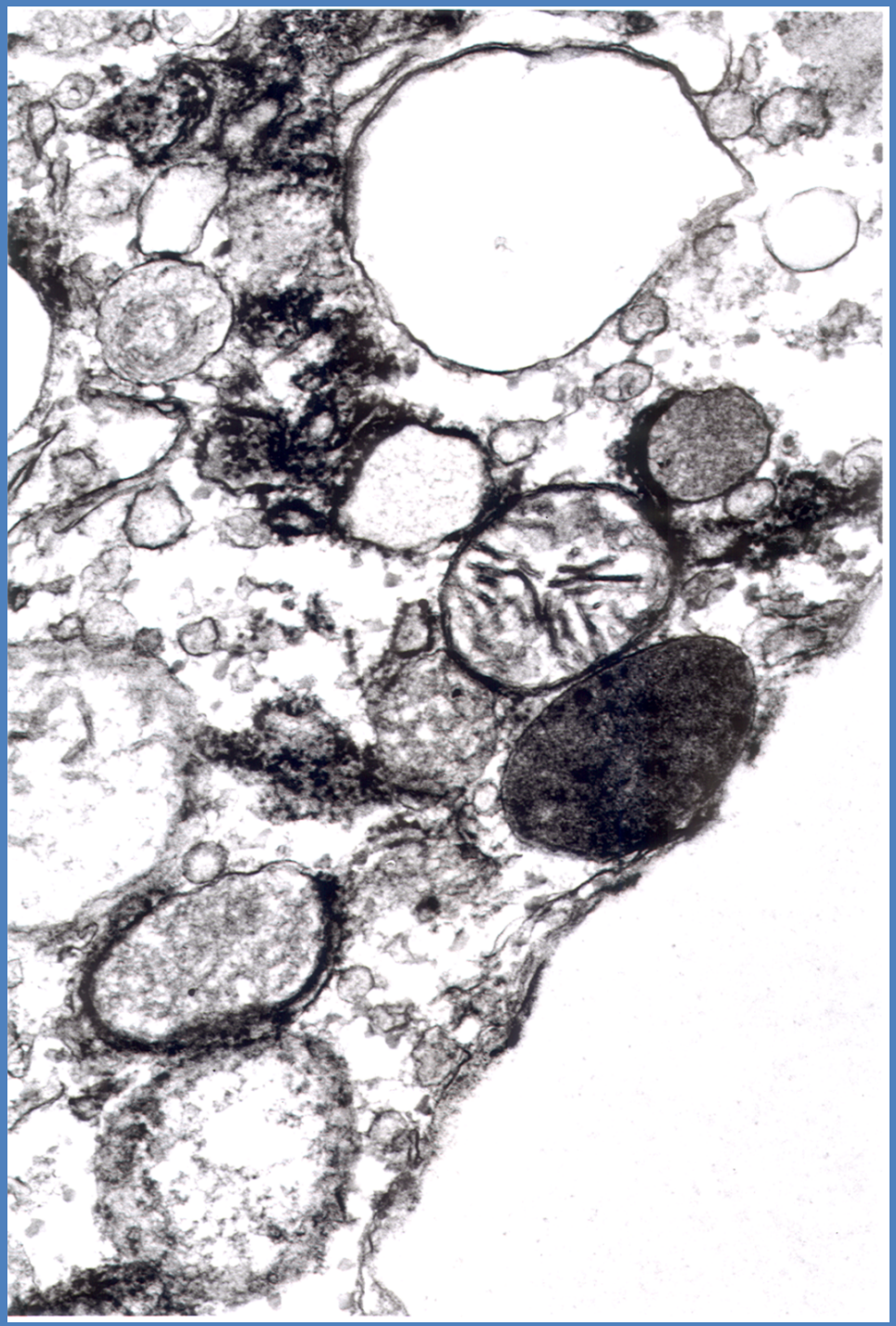








QUESTIONS

- How reasonable and practical would it be for professionals involved in fetal/perinatal death to effect a ***cultural*** change in our society so as to make autopsy a ***standard*** part of medical care for ***all*** who have lost a baby?
- Would it not be highly desirable for all trainees in medical genetics to have experience in fetal/ perinatal pathology?
- Or for pediatric pathology fellows (1 year!) to be trained also in developmental genetics and developmental pathology?

T.C. HSU – LIVING HISTORY BIOGRAPHY

"Frankly, I have only a moderate degree of intelligence…"

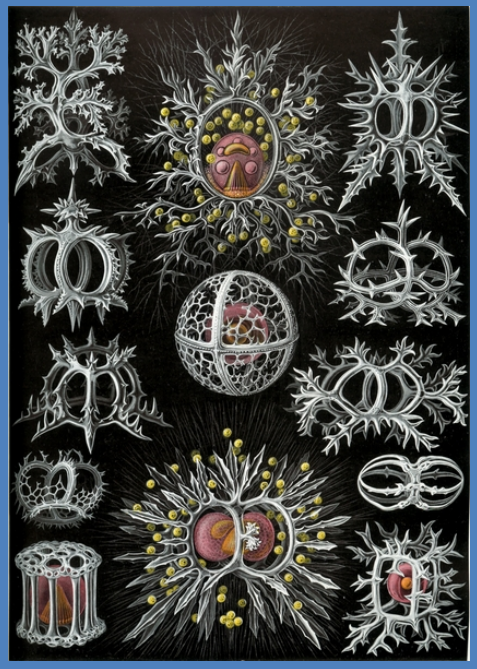
"I have published more than 300 articles, including 12 books. Some…were of good quality, some were mediocre, and others pure trash…Some papers in my own judgment were scientifically very good, but few people remember them."

(VALE) FAREWELL

Thus, in a brief lifespan, it has been my very great honor and privilege to attempt an ***understanding of human development*** (in essence not much different from that of the Julia Creek Dunnart) and of ***human evolution*** (in essence not much different from that of the chimpanzee), for…

VALE (FAREWELL)

… we and all our fellow creatures, from the smallest to the largest, are of identical root, thus, equally worthy of respect and reverence as a single family.*



Haeckel's Radiolarians

*q.v. Kaufman SA: Reinventing the Sacred 2008, and Suzuki D: The Sacred Balance, 1997