

The Arrogance of Teratology

Josef Warkany Lecture

58th Annual Teratology Society Meeting
Clearwater, FL

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24 June 2018



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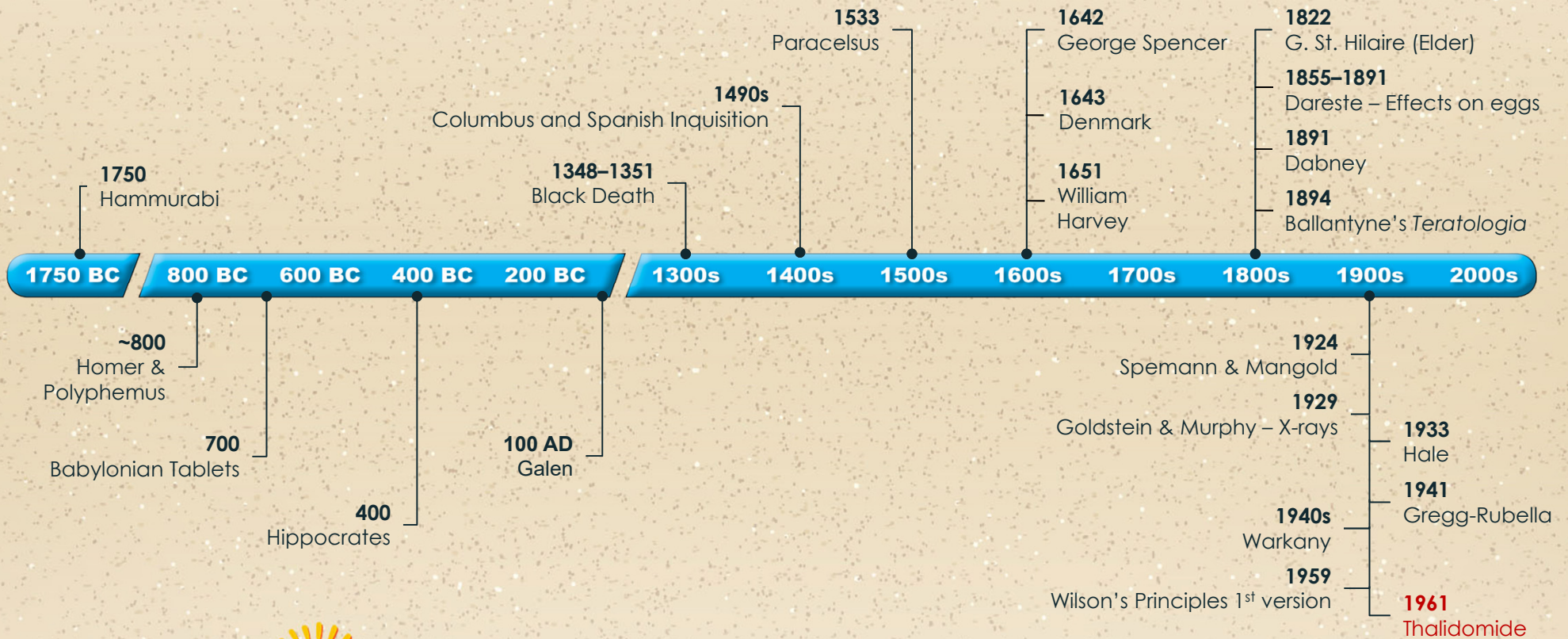
Teratology

The **scientific** study of the **causes, mechanisms** and manifestations of congenital malformations and neurobehavioral/physiological disorders with the goal of eliminating or ameliorating the conditions

Contextual meanings strongly influenced by:

- Contemporary state of knowledge or understanding
- Religious tenets of the period
- Philosophical ideologies

Timeline of History and Teratology



Ancient Teratology

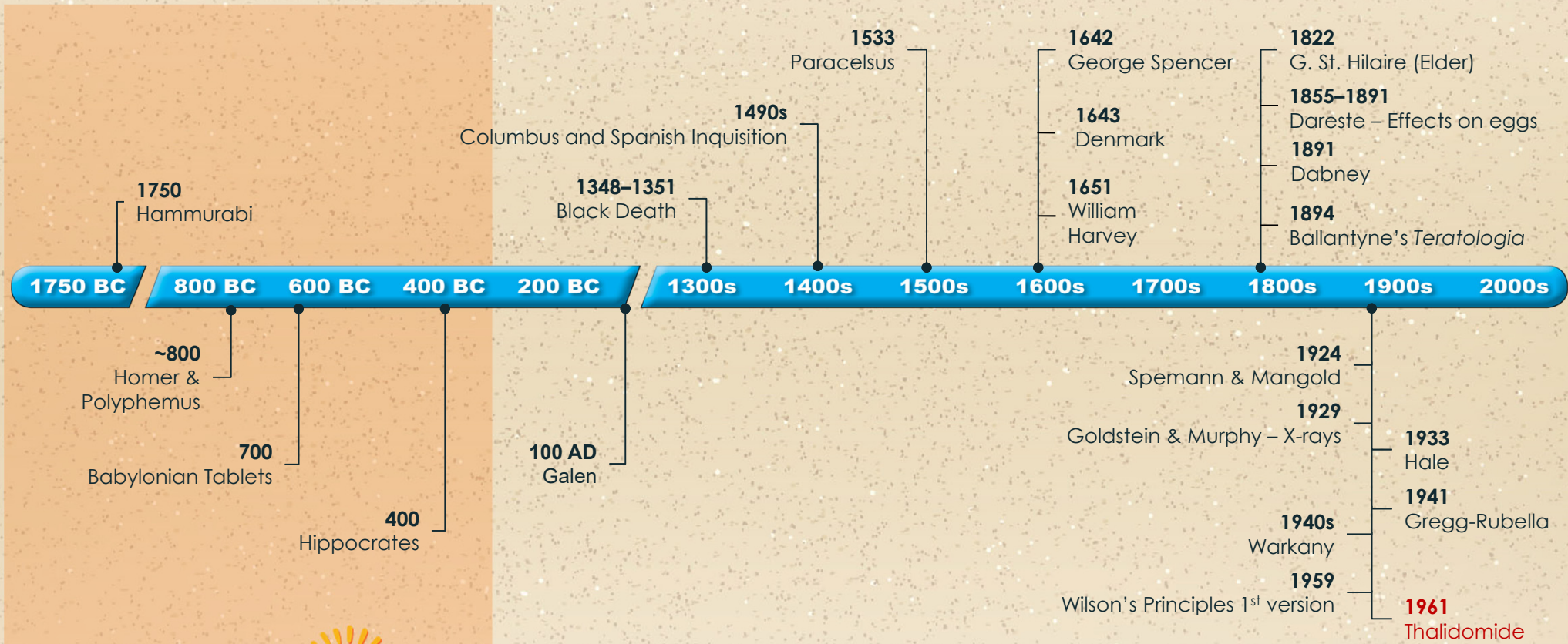
Portents and Hybrids



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Timeline of History and Teratology

Hybrids/Portents

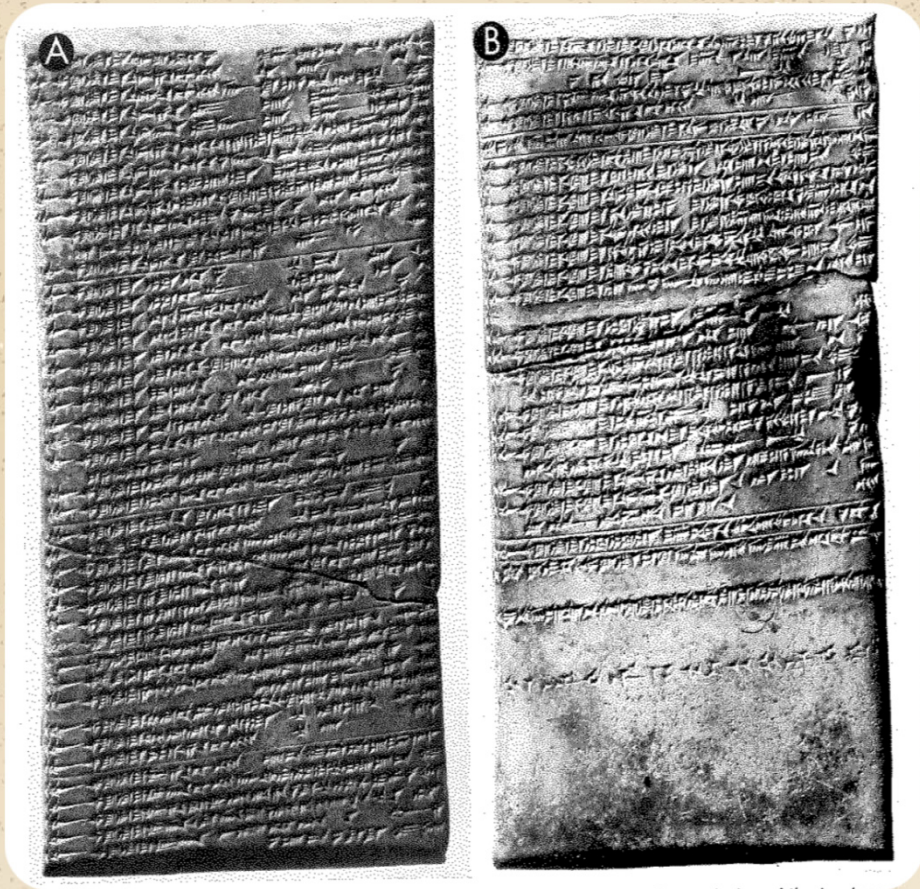


Where are we now?

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Ancient Teratology

Observations - Portents



Malformation

Infant with absent feet
Infant born with teeth
Infant with 6 toes / foot

Prediction

Canals will be ruined
King will live long and prosper
Kingdom will occupy
neighboring lands

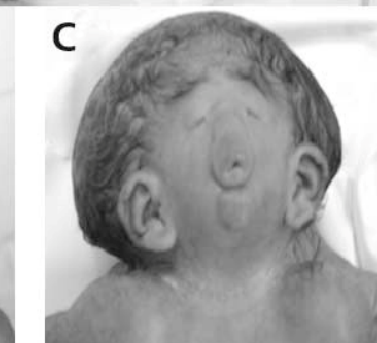
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Ancient Teratology

Could craniopagus (janiceps) have inspired configuration of the Roman god, Janus?



Janus: God of beginnings and endings, gates, transitions



T

B

Images of Multi-Limbed Hindu Deities



Kali Goddess of Death



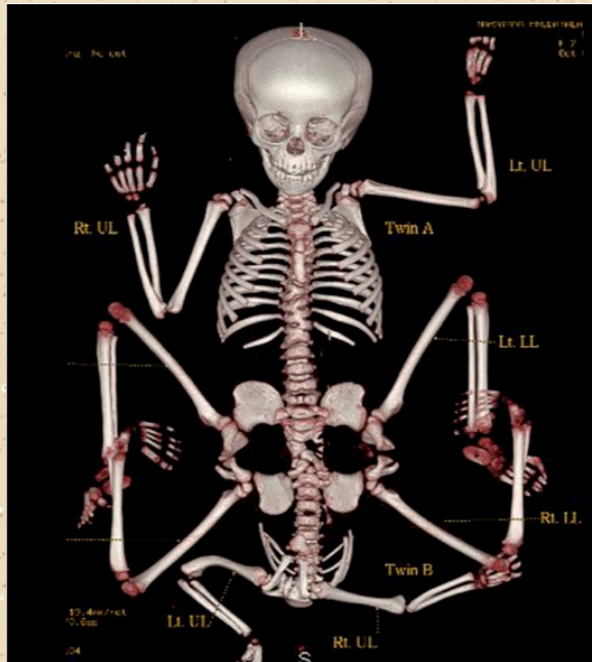
Durga Protector of Universe



Ganesh

Ancient Teratology

Parasitic twins may have influenced concept



Ancient Teratology

Greco-Roman Era

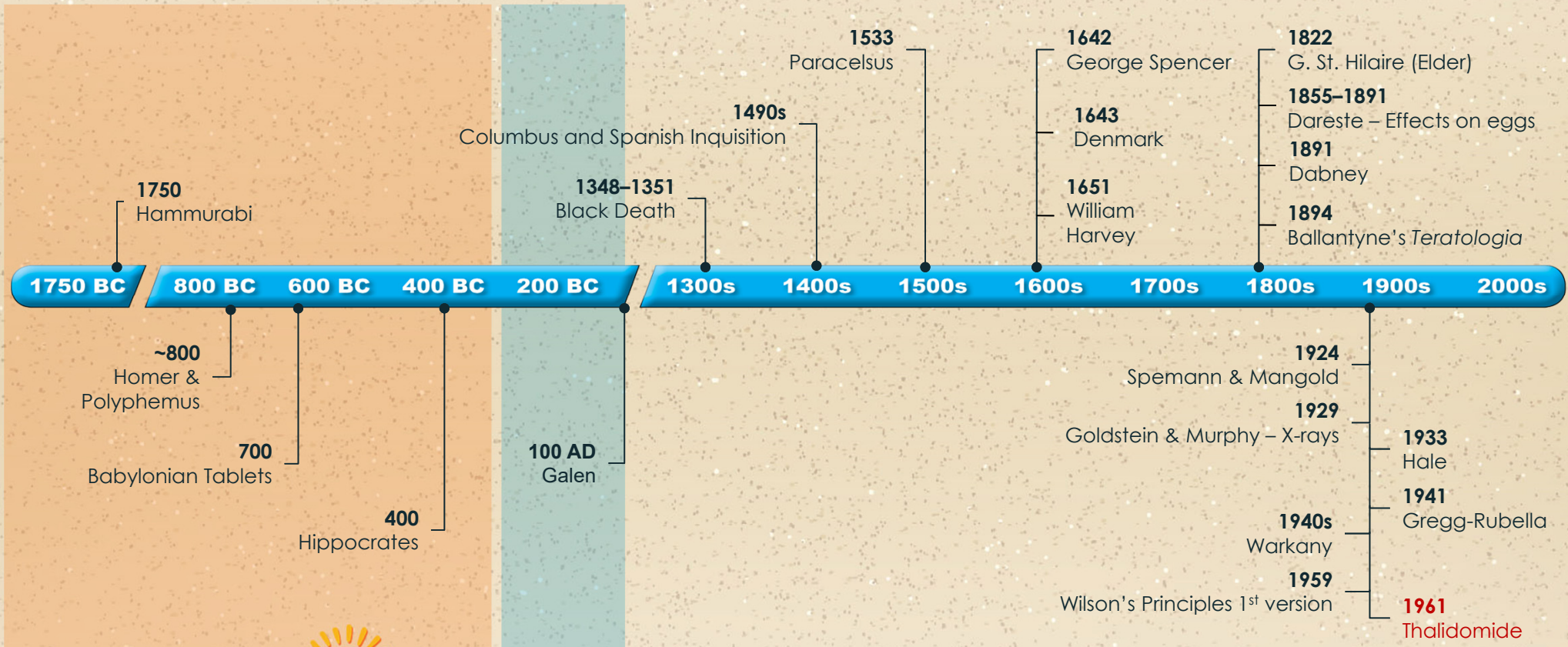


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Timeline of History and Teratology

Hybrids/Portents

Infanticide



Where are we now?

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Romans & Greeks - Infanticide

- Aristotle: “As to the exposure of children, let there be a law that no deformed child shall live.”

Fate of the Malformed

Infants were not considered individuals until a ceremony (~PND 10)

- Head of household (or a committee of elders) decided whether or not to raise the child
 - Economics (including sex)
 - Birth defects
 - Illegitimacy
- Exposure of unwanted
 - Clothed, often with “crepundia,” at public location
 - Hopeful of adoption (foundlings)
 - In the bush (often unclothed)



Dark Ages and Early Renaissance

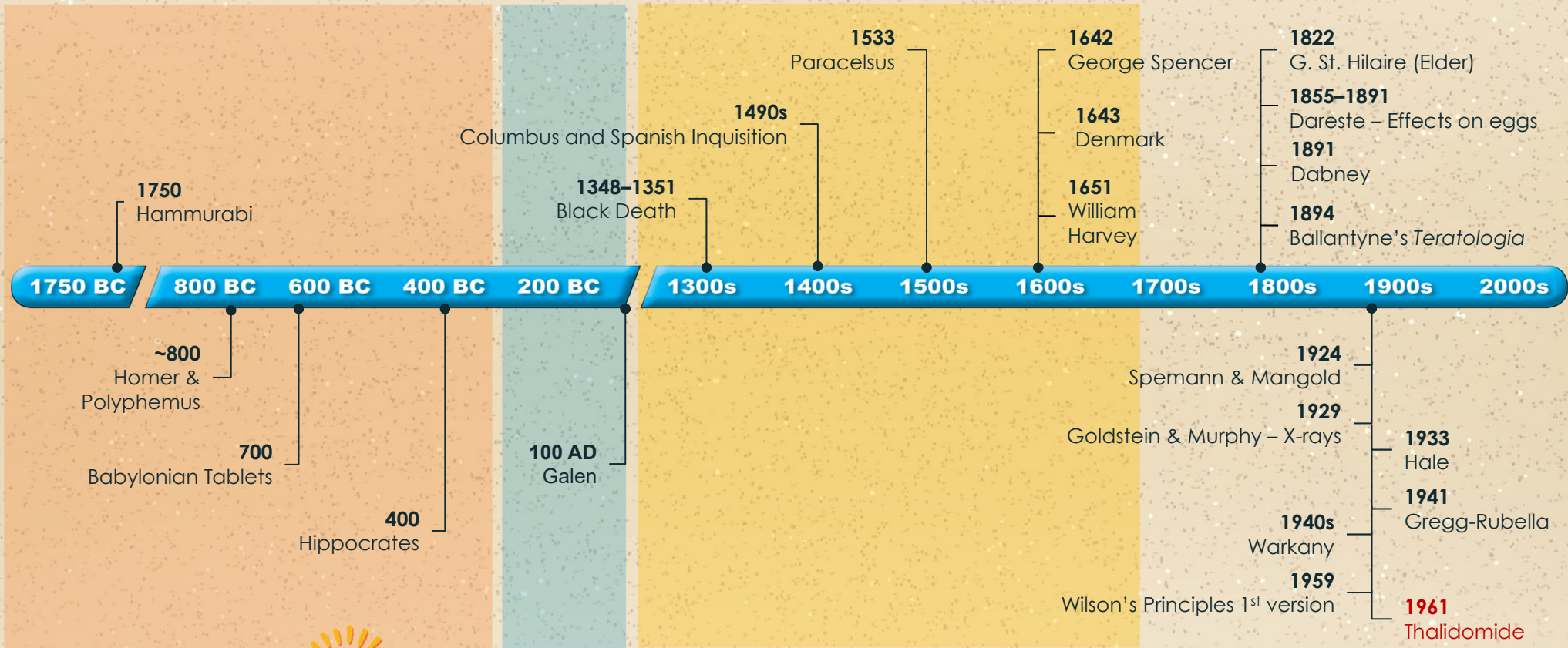
Demonic Influences

Timeline of History and Teratology

Hybrids/Portents

Infanticide

Demonic Influences



Where are we now?

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Prevailing ideas

- Human body is imperfect
 - Should be kept hidden
- Diseases and plagues due to God's wrath
- Deformities
 - Work of the devil
 - Punishment from God

Human Intervention and Rationale



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Case of George Spencer

New Haven, 1642

- Described as a balding, ugly servant
 - One glass eye and the good eye may have had a cataract
- Said to be a man of “lewd spirit”
 - Previously convicted of receiving stolen goods
 - Declined to pray
 - Read from the Bible only when his master ordered him to do so
- Worked for a time on a farm that raised pigs
- Left that farm for another employer
- At some time thereafter a sow gave birth to a cyclopic piglet
 - The single eye had a cataract
 - Given Spencer’s one (cataractous?) eye, bestiality was suspected
- **Both Spencer and the sow were put on trial**



Sow was tried first



TRIAL OF A SOW AND PIGS AT LAVEGNY.

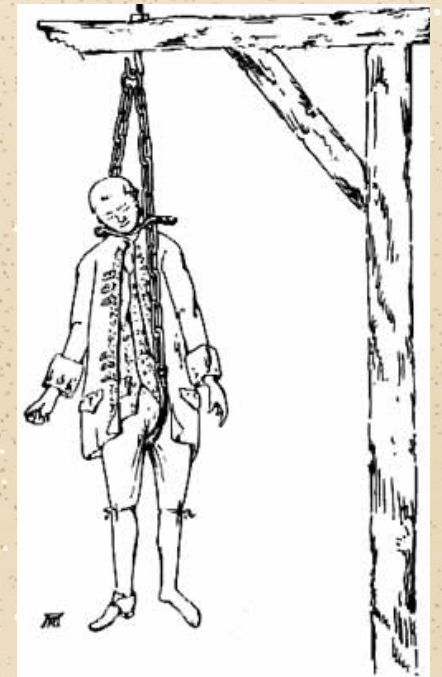


Execution of a Sow.

Conviction led to the sow's execution

Fate of George Spencer

- Under torture Spencer confessed; then recanted
- More cycles of torture, confession, recanting
- Conviction for a capital offense required 2 witnesses
 - His first confession was used as one witness
 - The sow was a second witness
- George Spencer was convicted and sentenced to death
- William Hogg was accused of similar charges (1645)
 - Hogg never confessed
 - He was spared due to lack of witnesses



Denmark, 1643

- A “strange” woman lived on the outskirts of a city
- She lived alone and did not socialize well
- She had several cats
- She gave birth to child “with the head of a cat”
 - Likely a premature birth of an anencephalic
- Bestiality and witchcraft were suspected
- She was tried and found guilty



Anencephaly

Fate of the Woman



~1,350 other Danes were convicted during the Burning Times (1540-1693)

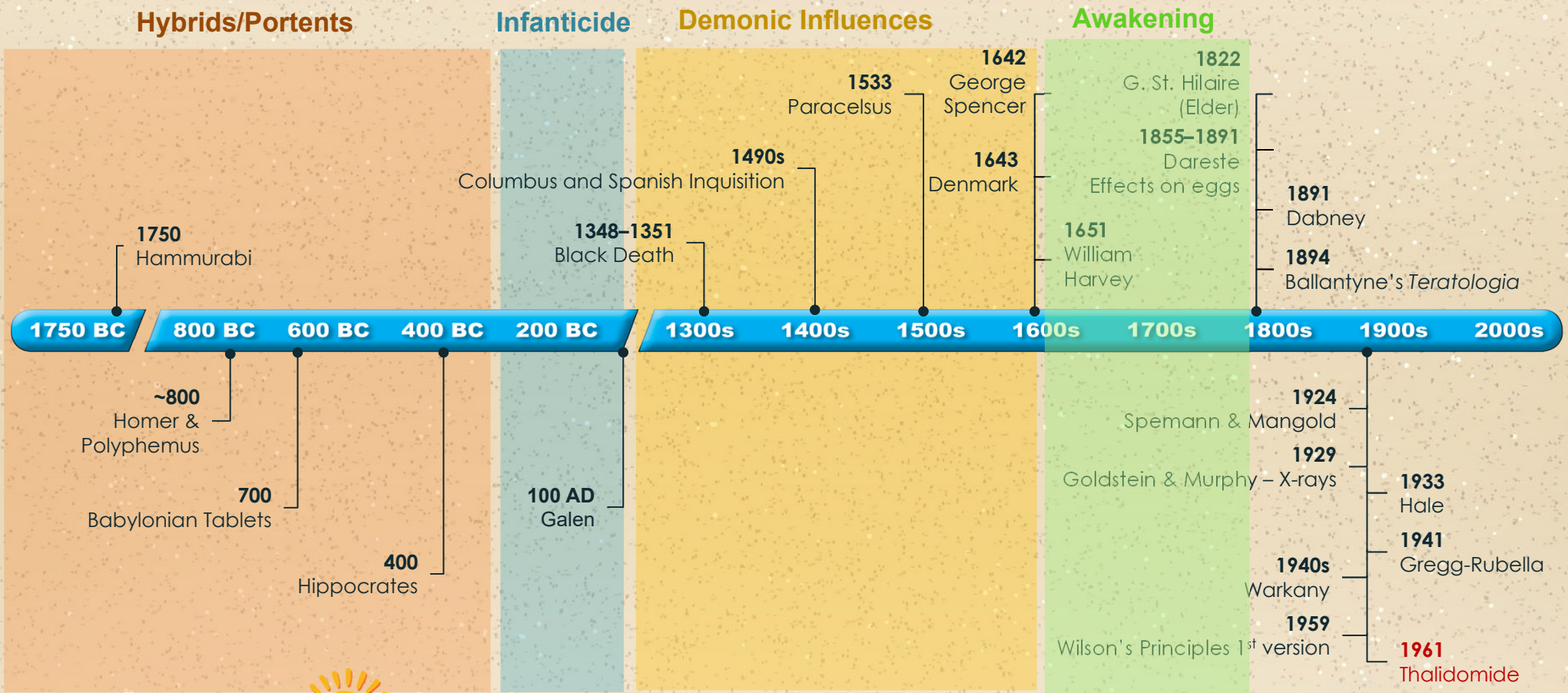


Awakening of Science Observers

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Timeline of History and Teratology



Where are we now?

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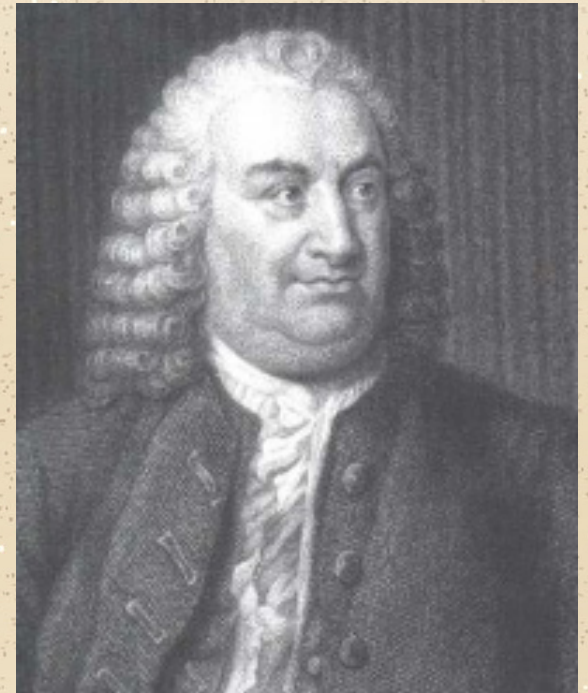
Preformation vs Epigenesis



Marcello Malpighi
(1628-1694)



N Hartsoeker
1695



Caspar Friedrich Wolff
(1733-1794)

Preformation supported the notion of divine wrath being visited upon parents of malformed infants

Etienne Geoffroy St Hilaire, the Elder

- Active in 1820's
- Perturbed chicken eggs
 - Physical prodding and shaking
 - Injection of various substances
- His work supported “epigenesis”
 - As opposed to preformation
- Laid groundwork of teratology
- Birth defects began to be scientifically understood as errors in developmental processes due to external influences rather than signs of demonic intervention



1772 - 1844



Awakening of Science Collectors

Clearwater Beach 

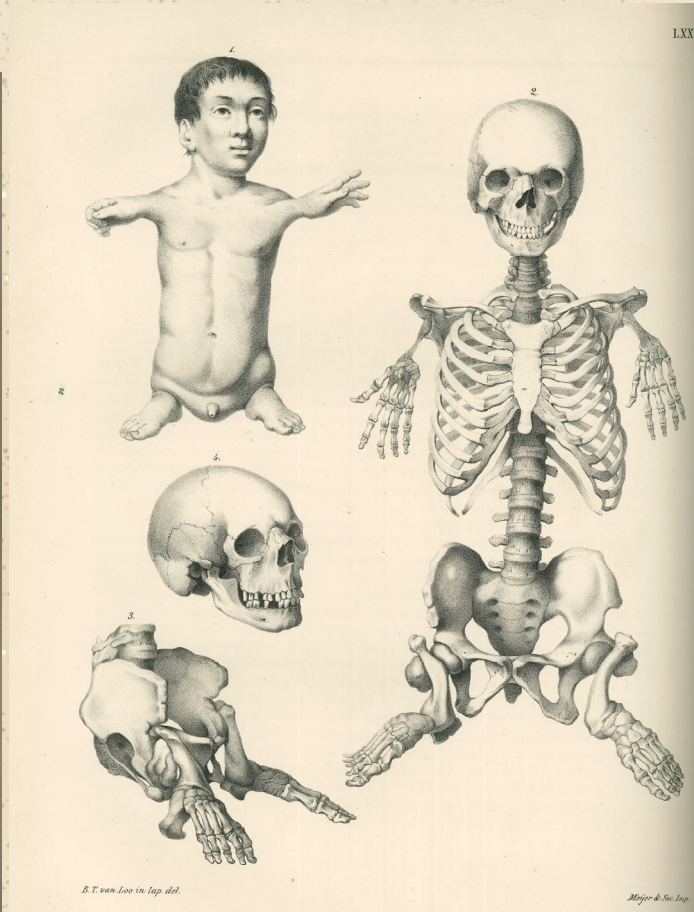
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Willem Vrolik



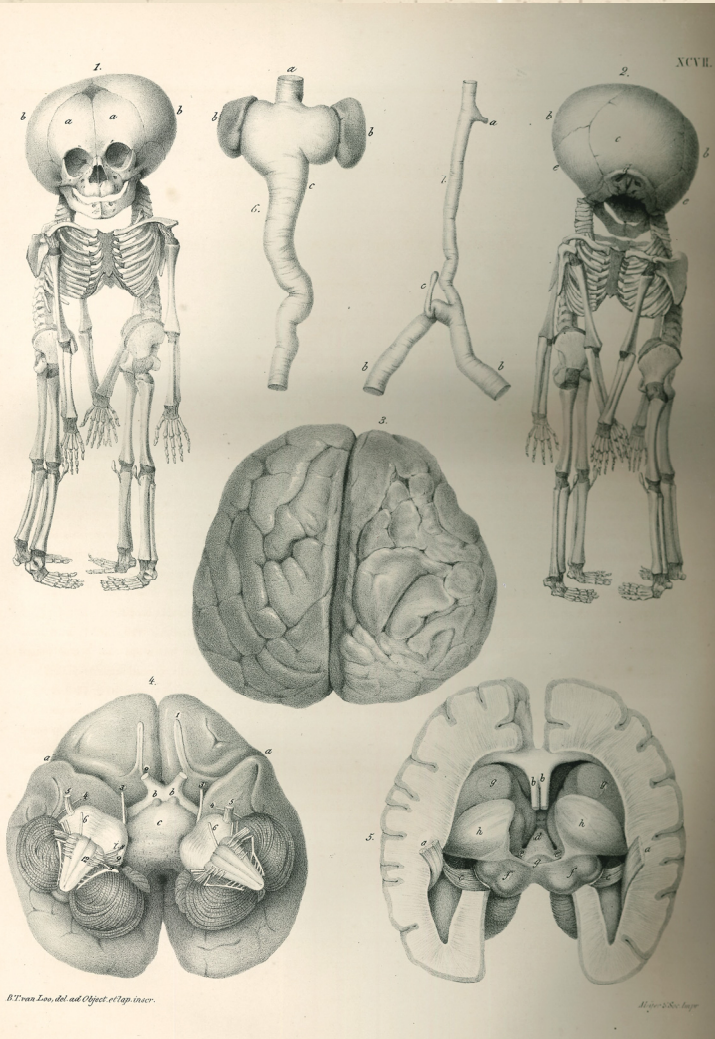
1801-1863

Dutch pioneer in
vertebrate teratology



Vrolik W. 1849. *Tabulae ad illustrandam embryogenesisin hominis et mammalium tam naturalem quam abnormem.*

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Body Snatch at the Firth of Forth

- **A prize specimen**
 - A hydrocephalic country boy died near London ca.1838
 - Family protected grave
 - After a month or so, things quieted down
- **Two Affluent visitors**
 - Well-dressed, cigar-smoking gentlemen in a horse-drawn cart
 - Request to tend the horse for an hour
 - A package expected; to be placed under the seat
 - Shortly, a livery man arrived and locked a package under the seat
 - The men returned and drove off briskly
- **The snatch is discovered**
 - That evening watchers found grave disturbed
 - Entire episode had taken less than 30 minutes!
 - Witness thought he recognized one of the men
 - Dr. Liston denied any involvement



Robert Liston

Flyleaf Illustration from Robert Liston's *Elements of Surgery* (1840)

Thomas Dent Mütter
wrote Preface to
American edition

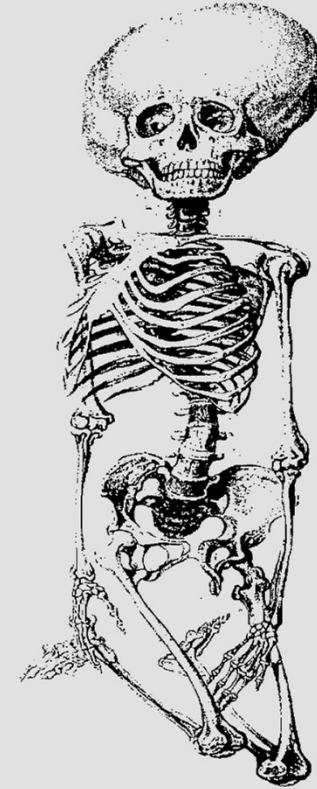


Fig. 1. A drawing on the flyleaf of Liston's book, *Elements of Surgery*, published 1840. Probably drawn from the skeleton of the hydrocephalic boy lifted from the grave near the Firth of Forth.

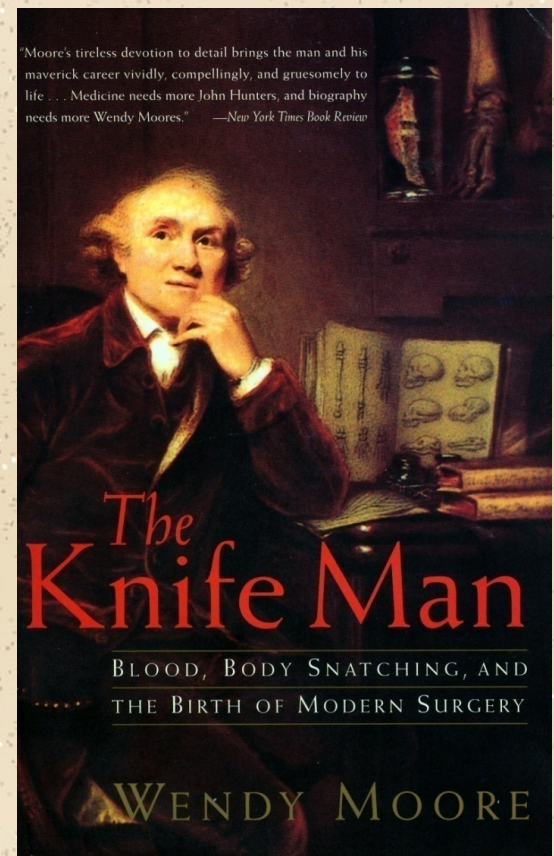
Body Snatching - Substitutions

- Bodies are not real property; vestments belong to heirs
- Undertaker often in on the job
 - Funerals for sand and rocks
- Charles Byrne (d. 1783)
 - Irish giant living in London
 - 8' 4" or 7' 10"



Body Snatching - Substitutions

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 - Funerals for sand and rocks
- Charles Byrne (d. 1783)
 - Irish giant living in London
 - 8' 4" or 7' 10"
 - The barn
 - John Hunter's cauldron
 - Disavowment



John Hunter (1728 – 1793)

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John Hunter's Collection



Text

eting



Awakening of Science

Early Mechanisms

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Camille Dareste (1822-1899)

Research on the Artificial Production of Monstrosities, or Essays on Experimental Teratogenesis (1876)

- Provided first well-documented evidence that neural tube defects were caused by failure of closure rather than bursting
- Outlined 5 principles of experimental teratology (foreshadowing and inspiring Wilson's Principles which appeared nearly a century later)



Maternal Impressions

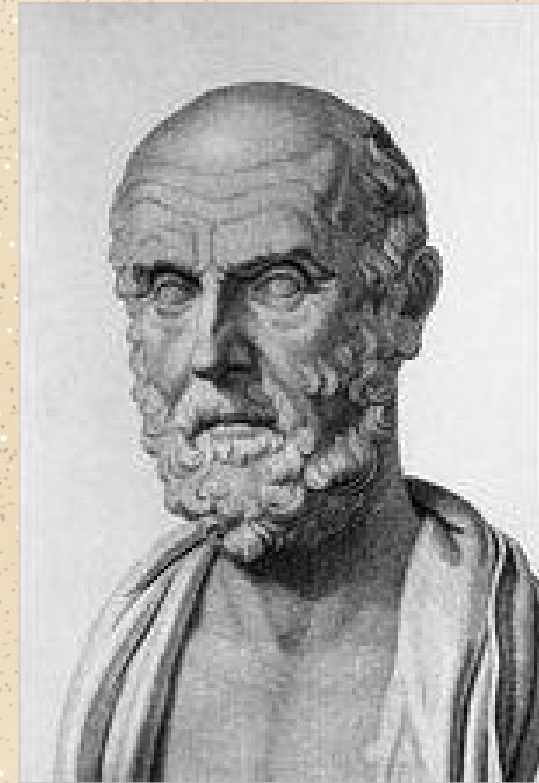


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Hippocrates and Maternal Impressions

Aristocratic woman of ancient Greece was tried for adultery

- Evidence against her was circumstantial, but strong
 - Both she and her husband were white
 - She gave birth to a dark-skinned child
- Hippocrates Came to court as she was about to be sentenced
 - Appeared on his own initiative as an expert
 - Stressed that:
 - ✓ She kept a picture of a Moor in her bedroom
 - ✓ During pregnancy she spent much time in her room looking at the picture
 - ✓ The child had a strong resemblance to the person in the picture
 - ✓ This had imparted a “maternal impression” that altered child’s color and body form
- Jury acquitted woman based on Hippocrates’ medical knowledge and highly regarded reputation



Hippocrates of Kos
(460-370 BC)

William C Dabney

“Maternal Impressions” (1891) in *Cyclopaedia of the Diseases of Children*, Vol 1, JM Keating, Ed., Lippincott Co., Philadelphia, pp 191-216.

Good points

- Cases excluded based on absence of specific stimuli
- Birth defects occur only after stimuli occur during first 2 months of pregnancy

Weak points

- Stimuli can include dreams
- Conclusion that maternal impressions cause birth defects
- Animals can be affected

William C Dabney (con't)

Text from his manuscript in a learned medium



“Abnormalities may occur in animals. This is not a valid objection, for animals possess emotions as well as Mankind...In Henderson, Kentucky there passed through the town a menagerie with which was an elephant; a sow pregnant a short time saw this elephant, and one of her pigs born some time afterwards had skin, ears, and *trunk* similar to those of an elephant... Now, unless we deny the facts, the conviction that the relationship... is that of cause and effect seems almost irresistible.”

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TERATOLOGIA:
A QUARTERLY JOURNAL
OF
ANTENATAL PATHOLOGY:

WITH
REVIEWS OF THE CURRENT LITERATURE OF
THE SUBJECT.

EDITED BY
J. W. BALLANTYNE, M.D., F.R.C.P.E., F.R.S. Ed.

VOLUME I.

WILLIAMS & NORGATE,
14 HENRIETTA STREET, COVENT GARDEN, LONDON,
AND
20 SOUTH FREDERICK STREET, EDINBURGH.
1894.

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John W. Ballantyne, MD

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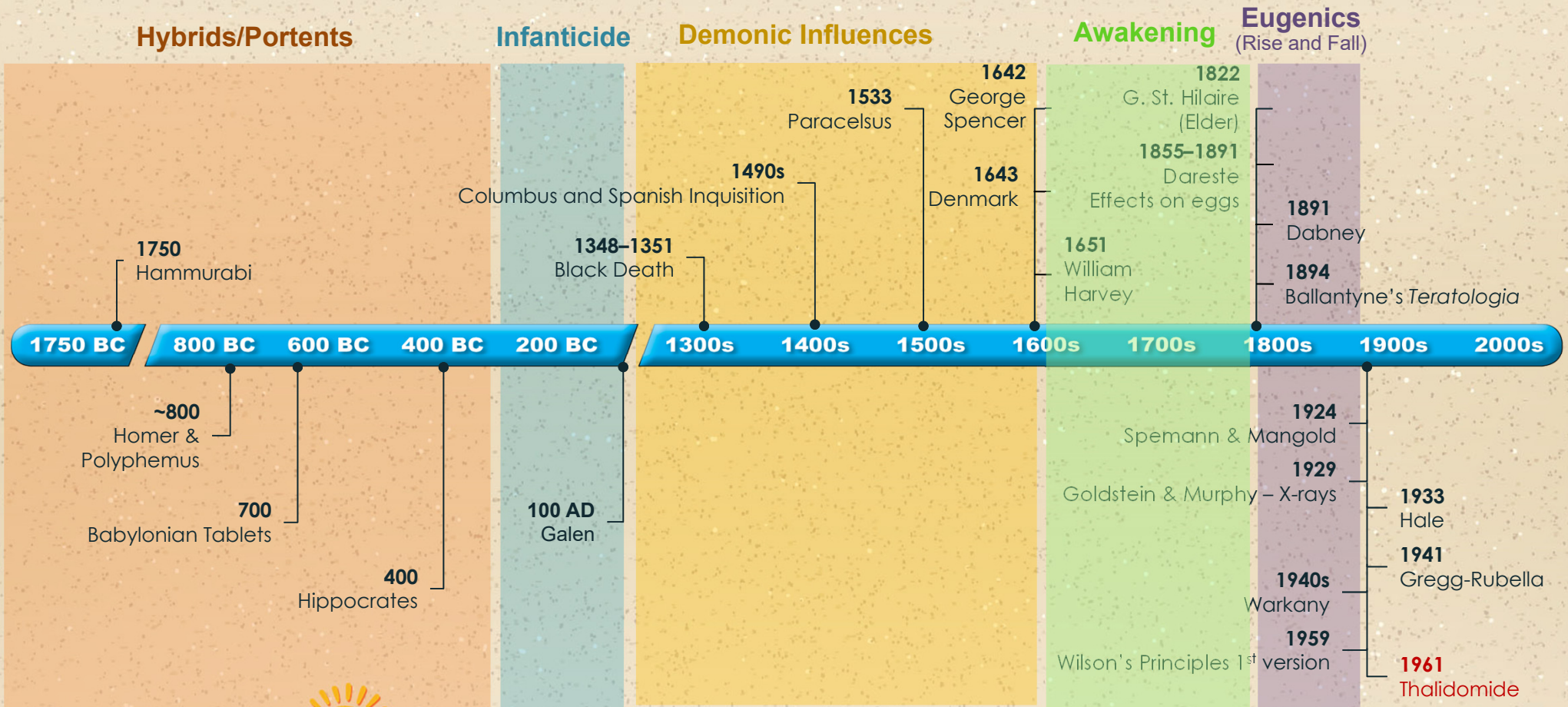




Eugenics

Rise and Fall

Timeline of History and Teratology



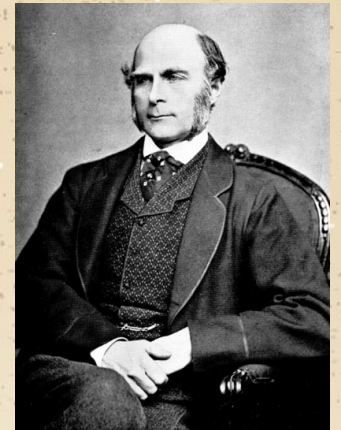
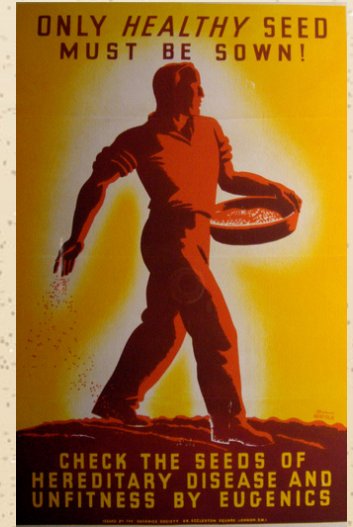
Where are we now?

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Eugenics

A set of beliefs and practices to improve the human genetic pool

- **Controlled breeding**
 - Among the “fit” to increase desirable heritable characteristics
 - Reduced reproduction/ sterilization of those with less-desired traits
- **Deep roots in history**
 - Espoused by Plato (~400 BC)
 - Popularized in late 1800’s by Francis Galton and William Goodell
 - In early 20th century spread across Europe, North America, and Asia
- **Concept fell out of favor after its perversion by the Nazis**



Francis Galton (1822-1911)

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Quotations of Early 20th Century Thought Leaders

Contemporary politics, beliefs and state of knowledge influenced the content of the following quotations

- The purpose of the quotations is to capture the sense of erudite people's thought at the time
- These quotes are out of context are meant neither to besmirch the memory of these individuals nor to vilify them in any way

Helen Keller

(Comments supporting a case of euthanasia)

“It seems to me that the simplest, wisest thing to do would be to submit cases ... to a jury of expert physicians. . . . They would act only ... where there could be no hope of mental development . . . We must decide between a fine humanity... and a cowardly sentimentalism.”



Theodore Roosevelt

“Society has no business to permit degenerates to reproduce their kind. It is really extraordinary that our people refuse to apply to human beings such elementary knowledge as every successful farmer is obliged to apply to his own stock breeding . . . We have no business to permit the perpetuation of citizens of the wrong type.”



Clarence Darrow

Known for defending the downtrodden:

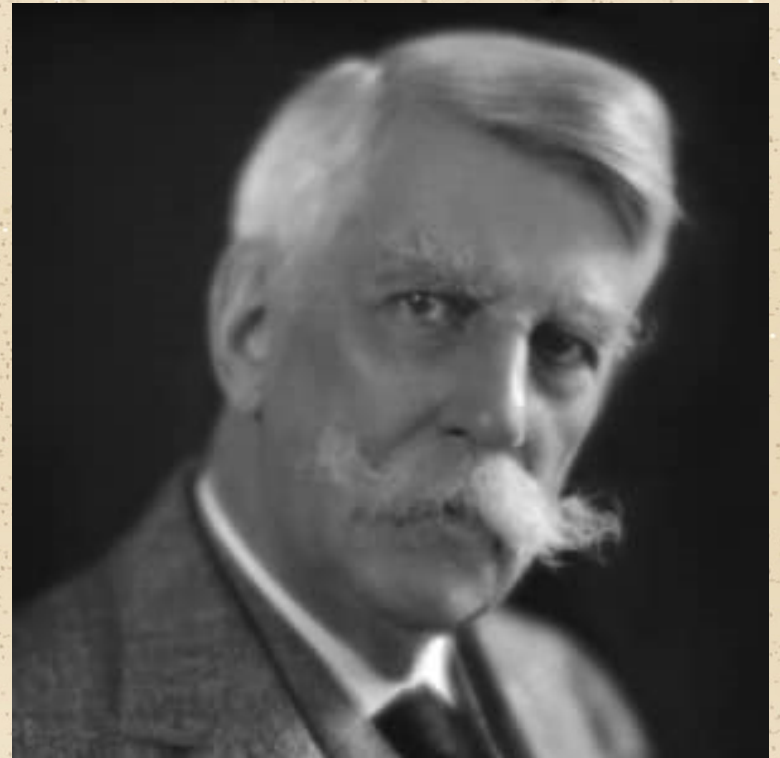
“You can only protect your liberties in this world by protecting the other man’s freedom”

“Show them the same mercy that is shown beasts that are no longer fit to live.”



Oliver Wendell Holmes, Jr

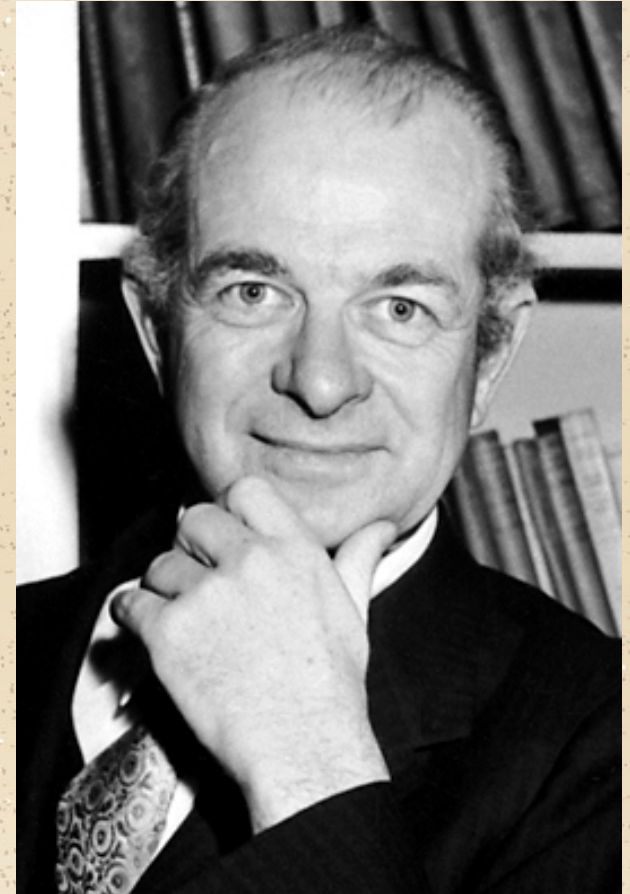
“It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind.”



Linus Pauling

Pauling found that sickle-cell anemia resulted from a mutation. He combined his findings with eugenics:

- He proposed mandatory genetic tests for African Americans
- Carriers of the disease would have restrictions regarding marriage and reproduction
- Suggested a prominent, visible mark be placed on carriers (such as a forehead tattoo)





Who would have been lost?

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1865-1923

Charles Proteus Steinmetz

Familial kyphotic dwarf with hip dysplasia
Nearly denied entry to US in 1889

Known for

- “The Wizard of Schenectady”
- Major contributor to nascent General Electric
- Responsible for making Alternating Current practical
- Ability to simplify complex issues into understandable, solvable problems



Einstein, Tesla, Steinmetz
(1921)

Matthias Buchinger: Phocomelic Overachiever



Lived: June 1674 – 17 January 1740

- 29" tall
- No legs or distal upper extremities
- No hands or feet

Amazing dexterity

- Built ships in a bottle
- Accomplished magician
 - Balls that disappeared/birds from nowhere
- Impressive displays of marksmanship
- Played numerous musical instruments
 - Dulcimer, flute, trumpet and more

Created incredibly detailed engravings

- Self portrait is an example
- Examine his curls closely
 - Microcalligraphy
 - 7 biblical psalms and the Lord's Prayer

Had a full "social" life

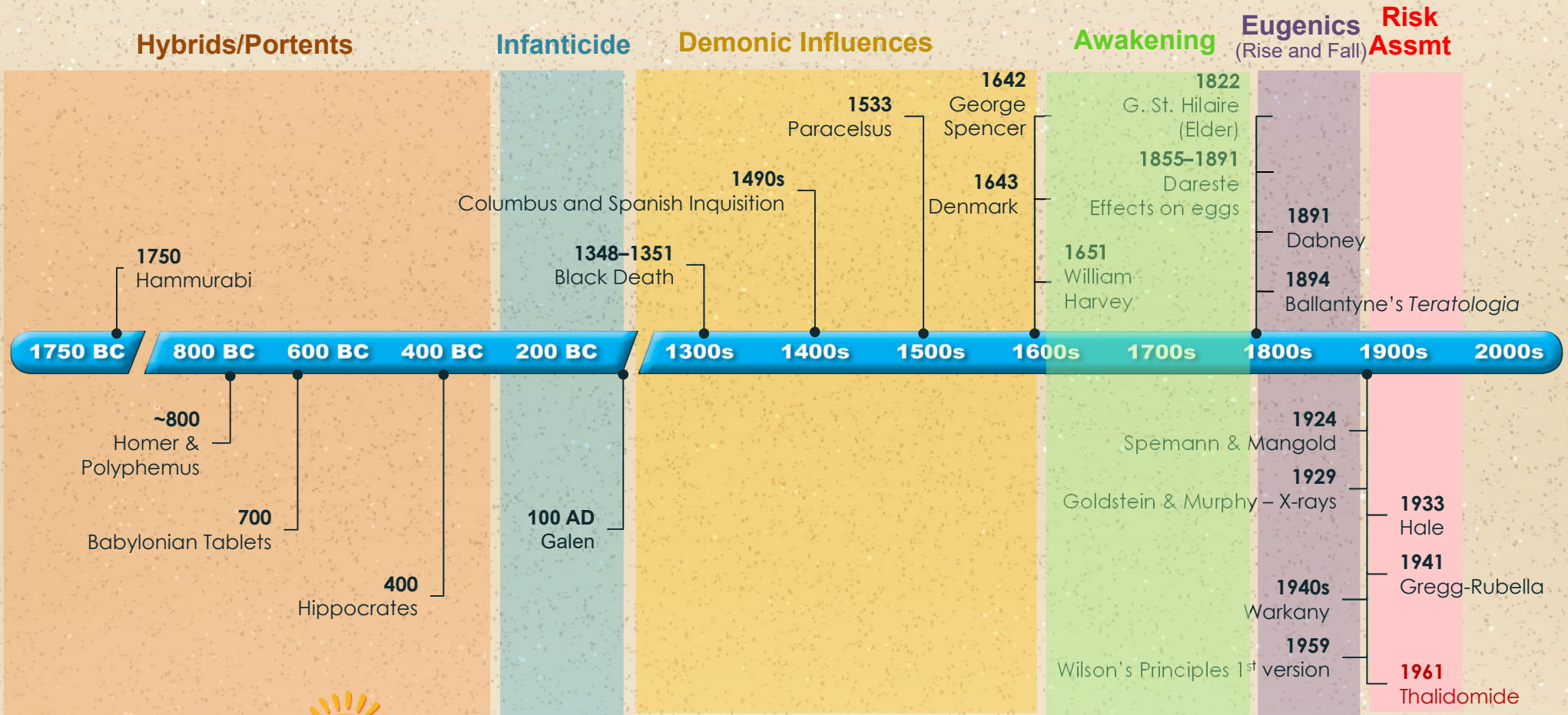
- Married 4 times
- At least 14 children by 8 women
- Rumored to have had ~70 mistresses
- Famed as a lothario
 - "Buchinger's boot" = euphemism for vagina



Thalidomide and Sequelae

Safety Assessment Era

Timeline of History and Teratology



Where are we now?

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Science Rises to the Challenge

- James Wilson's first set of Principles (1959)
- Teratology Society founded (1960)
- Thalidomide episode recognized in literature (1961)
- Goldenthal Guidelines (1966)
- Gene-environment interactions recognized as causal

Complexity Ensues - Testing

- Numbers of animals on test (~1200 in EFD alone)
- Enormous number of chemical and drugs that need to be evaluated
- Paucity of well-trained, experienced scientific staff
- New testing paradigms to reduce animal usage and time

Complexity Ensues – Understanding the Biology

- Gene-environment interactions
- Signal transduction pathways and the roles they play
- Assisted Reproductive Technology (ART)
- *In utero* therapies arise
 - Surgery

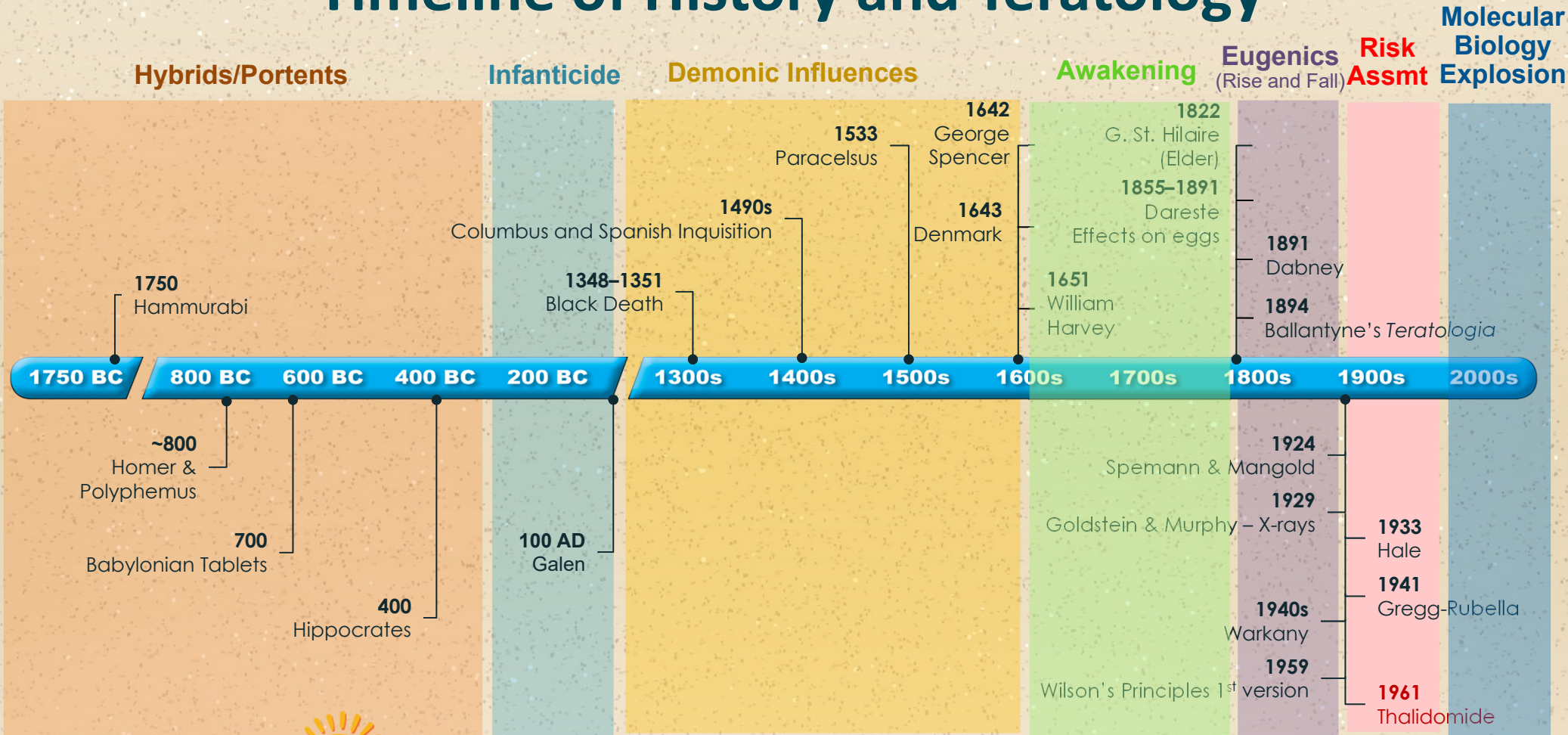
Molecular Biology and Informatics Explosion

Ethics and the 3 R's



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Timeline of History and Teratology



Where are we now?

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Gene Editing



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Identification of Genes with Specific Roles



Belgian Blue Bull

- Caused by a single mutation
- Myostatin gene (GDF8)

Use of CRISPR/Cas9 Technology

- Mutated myostatin gene (GDF8) in Belgian Blue bull isolated
- Mutated gene was inserted into an embryo derived from Nellore cattle
- The animal with the mutated gene (on right) exhibited significantly more muscle compared to its non-mutated twin

Comparison of twin Nellore cattle



Control

Twin with mutated
myostatin gene

Could this be done in humans?

- Screening for genetic mutations in conjunction with assisted reproductive technology (ART) has been used to prevent occurrence of babies with incurable, fatal diseases.
 - Example: glycogen storage diseases such as Tay-Sachs
- Gene editing has reportedly been tested in China to correct certain conditions
 - Examples: Certain (unspecified) cancers; HIV
- Is it ethical to use these techniques to “improve” offspring?

Regardless of the ethics, would you decide for your child to be an unnaturally conspicuous physical specimen?

(A National Academy of Sciences expert panel has warned against using the technology to enhance health or other traits but found it permissible to correct disease)



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Simplified Cell-based Testing Systems



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Novel Short-term Tests

Positive attributes

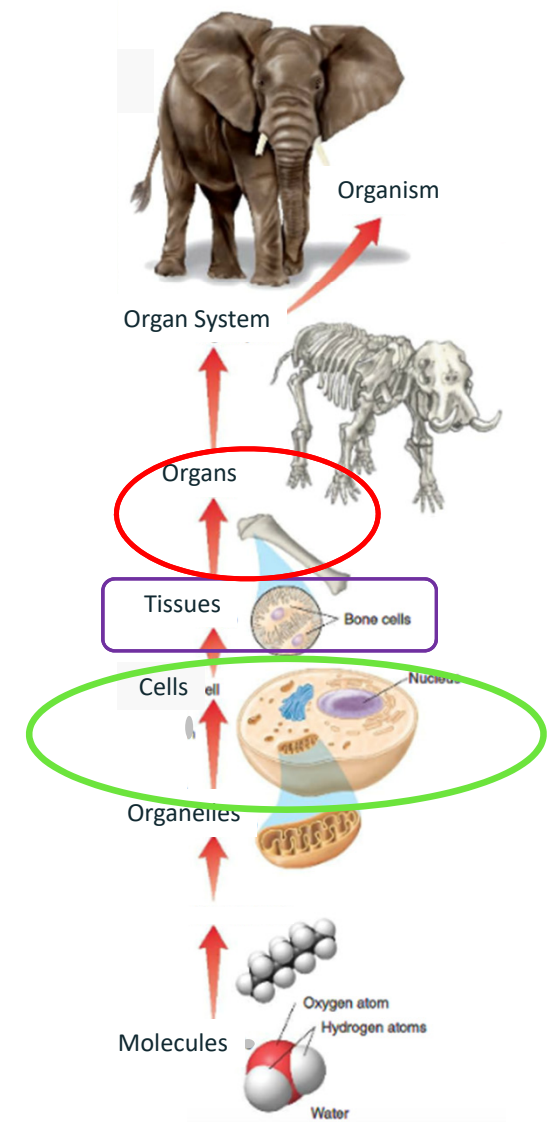
- Relatively inexpensive
- Much faster to run
- Greatly reduced numbers of animals
- Often provide mechanistic insight

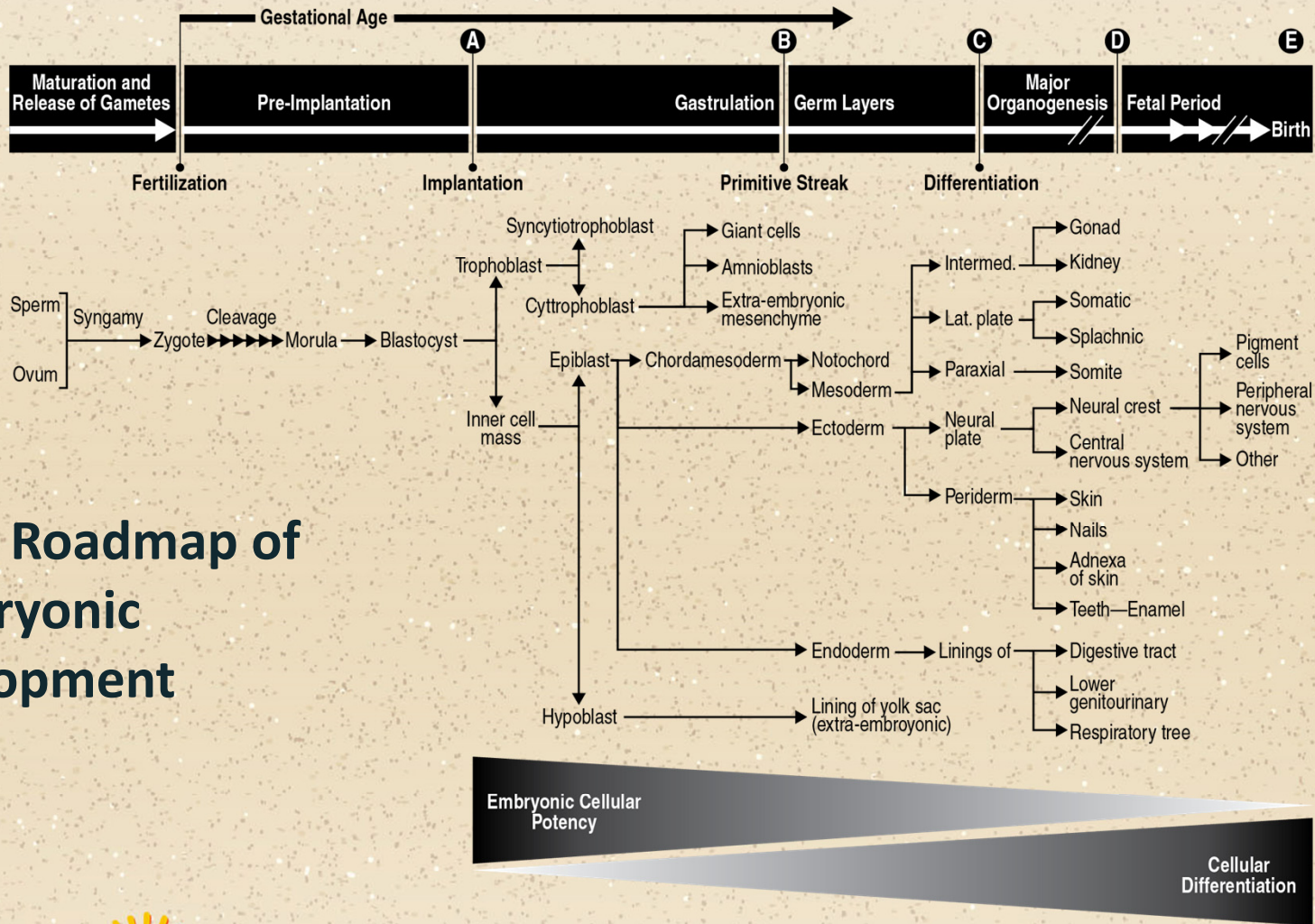
However...



Levels of Biological Organization

- **Molecules** – Combinations of atoms
- **Organelles** – Discrete subunits performing vital functions within cells
- **Cells** – Smallest unit of life
- **Tissues** – Groups of similar cells that perform a specific activity
- **Organs** – Structures typically composed of several types of tissues assembled to perform a physiologic function
- **Organ System** – Two or more organs functioning in unison to execute a specific bodily capacity
- **Organism** – An individual living thing that is composed of multiple organ systems and is capable of living autonomously





Source: DeSesso (2005)

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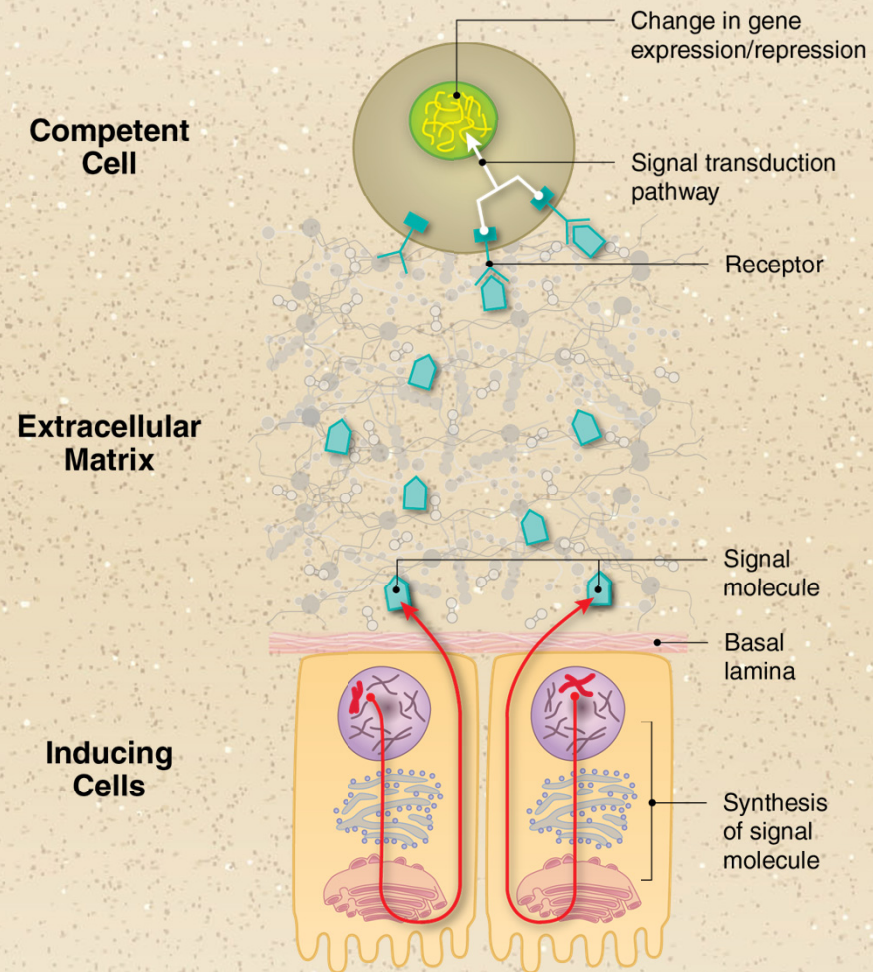


Conceptual Roadmap of Embryonic Development

Tissue Interactions

- Two cell populations
- Spatial proximity
- Message sent by inducer
- Message received by competent population
- Change in developmental state

Maturational
Stable



Novel Short-term Tests

Weak points needing continued development

- Unable to capture perturbations in cell-cell interactions
- Extracellular matrix effects are not discerned
- Disturbances in vascularity cannot be detected
- Temporal changes in differentiation and metabolism are not be tested
- Compensation (embryonic regulation) cannot be assessed
- Maternal influence and placental transport are not accounted for

However...



Novel Short-term Tests

Assessment and Future

- These test methods are not mature (yet)
- Must not expect too much from them – give them time to develop
- Results can be combined with bioavailability-based assessment data
- Will contribute to an integrated strategy that can winnow the number of chemicals needed to be tested and the number of animals to be used

Conclusions

The history of “Teratology” in various eras is replete with arrogance:

- Willingness to eliminate the malformed and punish their progenitors
- Zeal for obtaining malformed specimens for study by unsavory methods
- Confidence in investigatory approaches that are faulty or unproven
- Interpretation of results and recommendations that were influenced by ambient social or political environments

As we add to the history of our discipline, let us be cautious:

- **Remain scientifically humble**
- **Keep our values pure**
- **Ensure our analyses are based on the data before us**
- **Continue to make incremental advances in the science**
- **Not fall victim to an overly optimistic or exaggerated sense of our accomplishments**

