



EST. 1960 AS THE
TERATOLOGY SOCIETY

The Rise of Regulatogens:

A Crisis of Insouciance and Dilettantism in the
Regulatory DART World - And How We Must Fix It

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Disclaimer

The opinions put forth in this presentation are those solely of the author and do not necessarily represent those of his employer (Exponent) or the Society for Birth Defects Research and Prevention

Purpose of the Robert L Brent Lecture

To facilitate the discussion of new and old teratogens as well as new and emerging topics in the field

Introduction

What Is a Teratogen?

Complexities of Teratogens

- Historically, substances that cause malformations in offspring when administered to pregnant mammals are teratogens
- But interactions between test agents and embryos are complex - and often counterintuitive



Medicines Recognized To Be Teratogens

- **Thalidomide**
 - Seemingly innocuous sedative/anti-nausea agent
 - Heart defects, phocomelia, and other malformations
- **Accutane**
 - Acne medication
 - Face, ear and hearing defects
- **Methotrexate**
 - Used for rheumatoid arthritis, psoriasis, other autoimmune diseases; breast cancer
 - Craniofacial, heart and limb defects
- **Chemotherapeutic agents**
 - Cause episodes of cell death resulting in skeletal, heart, and other defects



Conversely, Some Teratogens Can Be Medicines

- Cyclopamine

- Alkaloid found in the corn lily that causes holoprosencephaly
- Inhibits expression of sonic hedgehog (Shh)
- **Repurposed** to treat glioblastomas that overexpress Shh

(Due to unpleasant side effects, analogs are being developed)

- Thalidomide

- Exerts anti-inflammatory and anti-angiogenesis effects
- **Repurposed** to treat multiple myeloma, leprosy, neovascular diseases including age-related macular degeneration

(Due to its teratogenic history, analogs are being developed)



Conclusions from the Preceding

- The pharmacologic landscape involving potential teratogens and reproductive life (especially pregnancy) is complex
- Before we talk about where we are going ...
Let's discuss how we arrived at the current situation



A Quick Look Backwards

What we knew...& when

- 1855-1891 – Dareste: Perturbation of chicken eggs and defects
- 1894 – Ballantyne's *Teratologia* (lasted only to 1896)
- 1929 – Goldstein & Murphy: X-irradiation & human birth defects
- 1935 – Hale: Vitamin A deficiency and absent eyes in piglets
- 1940's – Warkany: Vitamin deficiencies and birth defects in rats
- 1941 – Gregg: Rubella and congenital cataract
- 1959 – Wilson: First version "Principles of Teratology"

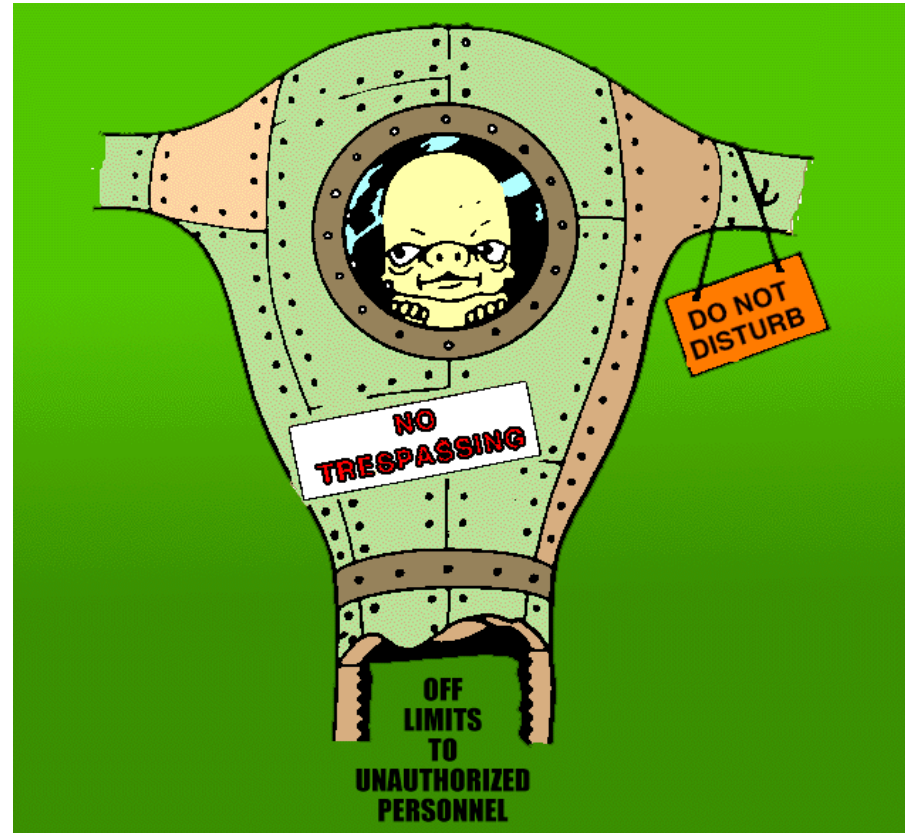
So, the knowledge was there...

BUT THE INTERNET WAS NOT



General Opinion at Mid-20th Century

- Regardless of knowledge in esoteric scientific literature - the medical community and the public believed the uterus was a privileged site



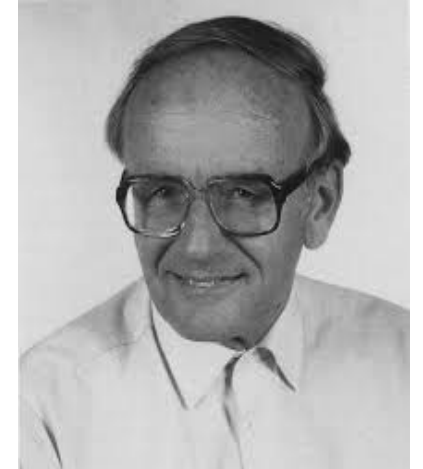
Cartoon by James Wilson

Then, along came Thalidomide (1958-1961)



William McBride
1927 - 2018

- Seemingly innocuous sedative introduced in 1957
- Marketed to pregnant women for morning sickness in 46 countries (mainly in Europe and Africa, but also Canada)
- Concerns regarding birth defects reported independently by Lenz & McBride
 - Estimated 10,000 - 12,000 malformed babies
 - Unknown number of deaths/terminations
- Not released in US due to the tenacity of a young, female reviewer at FDA who required safety data: Frances Kelsey



Widukind Lenz
1919 - 1995



Frances Oldham Kelsey
1914 - 2015



Amidst the Crisis – Founding of the Multidisciplinary Teratology Society (1960)



James G Wilson (2)

Josef Warkany (1)

F Clarke Fraser (3)

Academicians, Physicians, Industry Pharmacologists, Epidemiologists



Karnofsky's Law

(1965)



David A Karnofsky (4/5)
1914 - 1969

Marjorie M Nelson (4)
1909-1962
[Did not serve]

A teratogen is a substance that, when given to a pregnant animal

- At the right time
- At the right dose
- To the right species

Can cause developmental abnormalities

Key concepts embedded within Karnofsky's Law

- The existence of a critical period (window of susceptibility)
- There is dose-dependence (suggesting a threshold)
- The existence of species-specificity
- By extrapolation, no substance is inherently safe (need for risk-benefit assessment)



Other Definitions and Activities

- A burst of scientific papers appeared in the mid-'60s reported malformations after maternal exposures to all kinds of substances in single-dose experiments using extremely high exposures. (Few papers addressed mechanisms)
 - “A teratogen is a substance that, when given to a pregnant animal, results in a paper”
- Goldenthal Guidelines (1966)
 - Result of several workshops held at venues around the country
 - Segments I, II, III (have withstood the test of time)
 - Required specialized education and training
 - Center grants were established at various universities



Specialized Training and Educational Skills

Technical

- Animal handling
- Dosing
- Necropsy
- Surgery

Scientific Foundation

- Reproductive physiology
- Comparative anatomy
- Fetal evaluations

Specialized Scientific Knowledge Base

- Toxicology
- Embryology
- Perinatal biology
- Epidemiology
- Teratology principles
- Discipline-specific statistics
- (Endocrinology)
- (Pharmacology)

Advocates for better training



Steve Harris



John Rogers



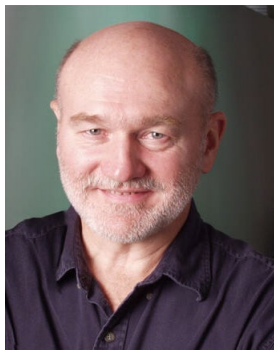
Bill Slikker



Tom Knudsen



Barbara Hales



Peter Wells



Cas Grabowski



Bob Kavlock



Marshall Johnson



Gary & Carole Kimmel



Melissa Tassinari
Melissa Tassinari



Jim Wilson



Dick Skalko



Joseph Holson

A Quick Look Forwards

What does “better training” mean?

- Future of developmental toxicity testing
 - *In vitro* and *in silico*
 - Mathematical and AI Models
- Modern academics and New Approach Methods (NAMs)
 - CRISPR-Cas9
 - Microfluidics
 - Organ-on-a-chip
 - Tissue/embryo culture
 - Knock out/knock in methodologies
- Pharma & crop protection companies
 - Great interest in NAMs



What problems *currently* face the regulatory community?

- Numbers of chemicals in commerce vs number of chemicals assessed
 - TSCA inventory (2026)^a
 - 86,741 chemicals (fewer than 1,000 fully assessed)
 - Pelley (2020)^b has estimated:
 - 157,000 chemicals
 - 75,000 mixtures and polymers
 - 120,000 substances not conclusively identified
- Large numbers of dossiers (EPA, REACH) with DART data available
 - There is a critical need for more reviewers

^a <https://www.epa.gov/chemicals-under-tsca/now-available-latest-update-tsca-inventory-6#:~:text=The%20Inventory%20contains%2086%2C741%20chemicals,portion%20from%20the%20confidential%20portion.>

^b Pelley (2020) *C&EN* 98(7)



WHERE DOES THIS LEAVE US??



What skills are needed to assess the extant data and present it to regulatory agencies?

- The previous list of specialized DART skills does not match with skills being learned in graduate training
- Where do folks in involved regulatory science learn all this?
 - Reading chapters in *Casarett & Doull* or *Hayes*?
 - Continuing Education Lectures
 - OJT (on the job training)
 - CRO's
 - Regulatory agencies (possibly - but not always)



The Bases for Many Current Regulatory DART Decisions

- Asterisks rather than biology
- Numbers of papers reporting a finding rather than quality of the underlying science
- Top-down decisions based on suppositions, opinions, and vagary rather than assessment of *all* validated data



Regulatogens

The results of poorly supported regulatory decisions made in the absence of scientific assessment are regulatogens

- Substances deemed to be teratogens/reproductive toxicants (or other toxicities) based on:
 - Opinion rather than science
 - Use of misinformation and unfounded theories for support rather than data
 - Validated by fear rather than assessment of risk
- Examples of regulatogens
 - Acetaminophen
 - Vaccines
 - Food-grade titanium dioxide (E 171)



An Unfortunate Sequela of the Regulatogen Crisis: Confirmation Bias



*HOW CAN WE FIX THE
REGULATOGEN CRISIS?*

Averting the DART Crisis and Phasing Out Regulatogens

Long-term remedies

- Targeted educational programs
 - Increased laboratory training
 - Increasingly difficult due to statutory issues regarding animal use
 - Targeted coursework
 - Comparative embryology
 - Comparative perinatal biology
 - Gestational physiology
 - Epidemiology (reproduction)
 - Discipline-specific statistics
- Drawback
 - This approach, while sound, will take years to diminish the crisis



Averting the DART Crisis and Phasing Out Regulatogens (*con't*)

Immediate remedies (*involve all of YOU*)

- Abandon the appalling silence and passivity when you recognize/complain about the regulatogen problem - but take no action

Apathy has a price!



Averting the DART Crisis and Phasing Out Regulatogens (*con't*)

- Challenge regulatory decisions that lack scientific rigor
 - Identify poor science and inappropriate interpretation of data sets
 - Emphasize that decisions should be based on high quality studies, not merely multiple matching mediocre studies
 - Provide (and defend) appropriately interpreted data and conclusions
 - Make explanations understandable to the regulatory community and the public
- Confrontation is *not* necessary
 - Small steps by many of us will make a big difference
- ***Do not wait for someone else to step forward***

SUCCESS BEGINS WITH YOUR ACTIONS, NO MATTER HOW SMALL



Conclusion

- In the absence of action (*especially by the knowledgeable and experienced members of this Society*), the crisis will escalate
 - Misinformed diletantes, obstreperous influencers, and vapid administrators will own the narrative
 - The Society for Birth Defects Research and Prevention will become a benign, feckless, and irrelevant clique
- We need to address the regulatogen issue head-on
 - We cannot rely only on a few leaders
 - *You* cannot sit idly by and expect success
 - *Everyone* must contribute in some way

The future of our Society and the health of our families depend on your actions!

