

Eminent Toxicologist Lecture Series

**From Murder to Mechanisms
7000 Years of Toxicology's Evolution**

Society of Toxicology

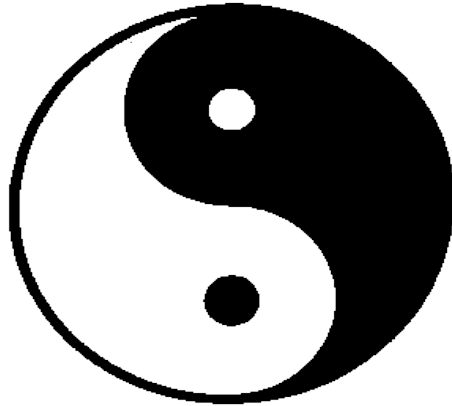
Eminent Toxicologist Lecture Series

7000 Years of Toxicology's Evolution

Michael A. Gallo, PhD, DABT (ret), Emeritus Fellow ATS
Professor Emeritus
Environmental and Occupational Health Sciences Institute
Rutgers-Robert Wood Johnson Medical School
Piscataway, New Jersey

Society of Toxicology

Toxicants: Friends or Foes?



“The dose makes the poison”

Paracelsus 1493-1541

Objectives

This presentation provides a history of toxicology with a few classic examples.

The Family of Toxicology

Poisons

Signs, Symptoms, Adverse Reactions & Antidotes

Drugs

Patent Medicines and Chemotherapeutics

Food

Natural toxicants

Industrial Chemicals

Occupational and Environmental Toxicity

Safety Evaluation

Hazard Identification

Tools to Elucidate Biology

Toxicology the Borrowing Science

- Pharmacology
- Pathology
- Physiology
- Biochemistry
- Synthetic Chemistry
- Analytical Chemistry
- Molecular and Cellular Biology
- High Resolution Imaging

Earliest Humans*

- Use of natural toxins
- Oral history evolved
- Animal venoms
- Toxic metals
- Plant extracts
 - Hunting*
 - Warfare
 - Assassination

* still used by indigenous people in S. America, Borneo, Pacific Islanders

Ebers Papyrus ~1500 BCE

- Hemlock
- Aconite (buttercup family)
- Opium
- Lead
- Copper
- Antimony
- Venoms

Hippocrates and Friends

- Defined effective dosages of toxin
- Described bioavailability
- Theophrastus (370-286 BCE)
 - *De Historia Plantarum*
- Socrates- Hemlock
- Dioscorides (Nero)poison classes through 19th
- Discovery of BellaDonna (scopolamine)
- Discovery of Digitalis (foxglove)Dioscorides

- Book of Job described Poison Arrows

Poisons as Suicidal and Murder Weapons

NCIS Romans

- Cleopatra and Marc Antony
- Wives of Senators and Caesars
- Nero and Britannicus
- Mithridates
 - Poisoning trials on prisoners
 - Developed 36 (?) ingredient antidote
 - Suicide after many tries
 - See *History of Toxicology and Environmental Health: Toxicology in Antiquity*. Ed. P. Wexler, Elsevier, Amsterdam, 2014 vols.1&2

Middle Ages Poets, Playwrights, and Assassins

- Shakespeare the Toxicologist
 - *Romeo and Juliet*: KCN & monkshod (buttercup) [R] belladonna [J]
 - *Hamlet*: Henbane (scopolamine & tropane alkaloids)
 - *Macbeth*: Double, double toil and trouble
- Florence & Venice—appoint official poisoners
- Lady Toffana: Arsenic cosmetics
 - Established dose and time relationship
- Spara: “Italian Widows Club” Arsenic for gold
- Borgias: Alexander VI, Cesare, Lucretia
 - Swelled coffers of the Papacy

Italy to France

- Catherine DeMedici
- Marchioness de Brinvilliers
 - Toxic mixtures tested on men and children
 - Described onset, potency, specificity, signs, symptoms and recovery
- Catherine Monvoison Deshayes
 - Midwife/sorcerer
 - “LaVoisin” killed ~2000 babies
 - Executed 1680

Paracelsus 1493-1541

- *“All substances are poisons. There is none that is not a poison. The right dose differentiates poison from a remedy”.**
- Mercury use for syphilis (+300 years); ether (Oil of Vitriol) as analgesic
 - *Defined the Toxicon: primary toxic agent*
 - *Experimentation and observation*
 - *Therapeutic vs. Toxic dose**
 - *Specificity of response*

Age of Enlightenment 17th & 18th Century

Strong Belief in Science

- Rammazzini: Occupational Diseases
- Pott: Scrotal cancer
- Magendie: Clinical and experimental pharmacology
- Claude Bernard
 - Experimental design
 - Use of controls
 - Early work on Endocrine system
 - Mechanisms of curare and carbon monoxide

The 19th Century

- Lincoln and Darwin born 2/12/1809
- Oswald Schmiedeberg 1838-1921 Physiologist/Toxicologist
- Louis Lewin 1850-1929 narcotics, methanol, CHCl_3 , TCE, glycerol
- Charles Darwin 1809-1882 Evolutionary theory
- Friedrich Miescher Discovered DNA in lymphocytes 1869
- Alice Hamilton Occupational Toxicology 1869-1970
- Harvey Washington Wiley , 1883 Chief Chemist–food adulteration

The 19th Century

- M. J. B. Orfila (1787-1853)
- “Father of Modern Toxicology”
 - Forensic Toxicology/Chemical analysis
 - Isolation of belladonna (scopolamine) & wolfbane
 - Multiple studies in lab animals, use of controls
 - Eloquent texts on Toxicology and Medical Chemistry
- Marie & Pierre Curie discover radium 12/26/1898
- Nobel in Physics 1903
- Marie Curie, Nobel in Chemistry 1911

Chemistry of the 19th Century

- 1820s Phosgene and Mustard Gas Synthesized
- 1850-1880 >10,000 novel chemicals
 - ChCl_3 , CCl_4 , ether, and carbonic acid (Lister)
- Asbestos major mining in U.S. ~ 1899
- Introduction of organic arsenical pesticides
- Petroleum byproducts, coal tar derivatives & aniline dyes
- **Harvey W. Wiley** appointed Chief Chemist, Bureau of Chemistry: food adulteration studies (1883)

Impetus for Toxicology in the 20th Century

Rapid advances in Biology, Chemistry and Medicine

Recognition of the toxicological sciences

Toxicant induced disasters were followed by:

- Animal models of toxicity

- Analytical chemistry advancements

- Clinical toxicity evaluations

- New Regulations

Toxicology in the Early 20th Century

- 1880-1910 Workers insurance laws
- Patent medicine frauds widespread
- Meat packing & other occupational scandals
- Div. Industrial Hygiene US PHS established 1914
- Chemical companies establish toxicology centers
- World War I (7/1914-11/1918) gas warfare*

*Phosgene, chlorine, sulfur mustard

Hayburn (Wiley) Legislation

- Upton Sinclair's *The Jungle* (*Meat Packing Regulations 1906*)
- Alice Hamilton Illinois Commission on Occupational Diseases (1908)
- Patent Medicines Claims
- Major battles with Patent Medicine Fraud “Dr. Munyan”
- What did Harvey W. Wiley Want?
 - No toxic Compounds *Especially ethanol and Color Additives*
 - Government Analytical Labs
 - Rigorous Enforcement
 - Toxicity Testing
 - Marketing Approval
- “Wiley” Bill (*The Food and Drug [Hayburn] Act of 1906*)

\$5,000 from Congress (1902) Starts the “Poison Squad”

*O, they may get over it but they'll
never look the same,*

*That kind of bill of fare would drive
most men insane.*

*Next week he'll give them moth balls,
a la Newburgh or else plain;*

*O, they may get over it but they'll
never look the same.*

"Song of the Poison Squad" (1903)
Lew Dockstader's Minstrels



Smithsonian Institute Archives

Wiley vs. Munyan (and the Courts)

- “We have cured thousands” *Munyan claimed*
- “I never thought Wiley (gov’t labs) would analyze our drugs”
- “None are cures” *Wiley*
- “Is Hype Misbranding”? *Munyan*
- *“Hype is not illegal” “False therapeutic claims not prohibited”*, Supreme Court (U.S. vs Johnson) 1911, overturns the Hayburn Bill, 1911
- Sherley Amendment, enacted 1912 to overcome 1911 Supreme Court decision, *prohibited false therapeutic claims*

1920– 1940 (1)

New Challenges and Modern Toxicologists

- PCBs developed as transformer coolants 1929
- Kallett & Schlink *100 Million Guinea Pigs* 1933
- DDT: Muller, 1939 (Nobel Medicine 1948)
- Phenoxy herbicides: Templeman 1940
- Marie Curie dies July 4, 1934 of radiation-induced pernicious aplastic anemia

Toxicology 1920-1940 (2)

- Diethylstilbestrol (DES), and Bisphenol A (BPA), other non-steroidal estrogens (Dodds et al 1936)
- Prontosil (Domagk 1932) [Nobel in Medicine 1939]
- Sulfanilamide “Elixir” 1937 (Diethylene Glycol)
- Food, Drug & Cosmetic Act (Copeland Bill) 1938
Safety and Efficacy before Marketing

Toxicology's Many Paths: Toxicology during 1940s

- World War II introduces the atomic age
 - **Organophosphates: Nerve Gases to Pesticides**
 - **Antimalarials: Mice to monkeys to man**
 - **Radiation Biology & the Bomb-metals toxicity**
 - **Herbicides (2,4-D & 2,4,5-T) for food and fiber**
- DES introduced into Clinical Use
- Federal Insecticide Fungicide Rodenticide ACT (FIFRA) 1947
- Artificial sweeteners & Weight loss craze
- *"Detoxication Mechanisms"* R.T.Williams 1947 Drug metabolism comes of age
- **FDA publishes *"Appraisal of Toxicity of Chemicals in Foods"* 1949 Arnold Lehman, editor**

Toxicology Gets Organized 1950-1960

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- 1956 1st GRC on *Toxicology & Safety Evaluation*
- 1956-59 Planning for SOT
- 1959 TAP : Coulston, Hays, and Lehman eds.
- 1959 DuBois and Geiling “Textbook of Toxicology”
- 1960 Delaney “clause” to FD&CA
- 1st hint of TCDD toxicity as phenoxy contaminant
- Pharma, AgChem & Food safety testing expands toxicology

Analytical Chemistry Improves Residue Testing

- 1910-20 PPHundreds
- 1920-40 PPThousands
- 1940-1960 PPMillion*
- 1960-1980 PPBillion
- 1980-2000 PPTrillion
- 2000-present PPQuadrillion**
- * **The Vanishing Zero** *Zweig 1972*
- ** **The Vanishing Zero in the Age of Genomics** *Zarbl et al 2010*

Toxicology's Exponential Growth 1960-1980

- Delaney Clause Prohibited food additives that “are animal or human carcinogens”
- DES transplacental cancer 1970 Drs. Herbst & Scully
- Thalidomide disaster 1960 Dr. Frances Kelsey
- Introduction of the “Pill” 1960 (1956)
- SOT Founded 1961
- Silent Spring Rachel Carson 1962
- Vietnam War (1964-1974) Agent Orange & TCDD*
*(toxicity related to an “orphan” receptor)

Toxicology 1970-1980

- NIEHS, NTP, NCTR, EPA, OSHA established
- Ames publishes early papers on mutagenicity
- Casarett & Doull's *Toxicology 1st edition* ('75)
- AhR and “orphan nuclear receptors”
- Introduction of GLP Guidelines
- “Superfund” sites identified
- Love Canal toxic wastes
- Times Beach, MO, TCDD contaminates town

Toxicology 1980- 1990

- Drug / Chemical Metabolism
- Focus on carcinogens and mutagens
- Endocrine Disrupting Chemicals
- Transgenic animals and Zebra Fish
- Industrial Disasters
 - Bhopal Explosion: Methyl Isocyanate
 - Chernobyl Explosion: Radiation

1990-Present

- Biomarkers of disease and exposure (exposome)
- Role of the microbiome
- 1994 Dietary supplements as foods
- 1996 Food Quality Protection Act eliminates pesticides from Delaney clause of FD&CA
- GMO crops introduced 1996

SOT 1980–Present

- Regional Chapters and Specialty Sections 1981
- GRC Mechanisms of Toxicity 1985
- American Board of Toxicology 1980
- Academy of Toxicological Sciences 1981
- Expansion of Graduate Programs
- SOT Expands membership to Associates and Students

Friends or Foes

- Aspirin and Acetaminophen
- Thalidomide 1960-1962... then and now!
- Dioxins and PCBs
- DES

Aspirin & Acetaminophen

- **Aspirin** discovered 1899 (salicylates in Willow bark; 1500 BCE)
- **Anti-inflammatory, Analgesic, Antipyretic**
- Gastric ulcers, bleeding, tinnitus, Reye's syndrome (> 1200mg/d)
- Cardioprotective (81mg/d)

- **Acetaminophen** discovered 1893; (Tylenol 1955)
- Lower doses (500-1000mg/d) very effective **A-A-A**
- High dose severe hepatotoxicity, death

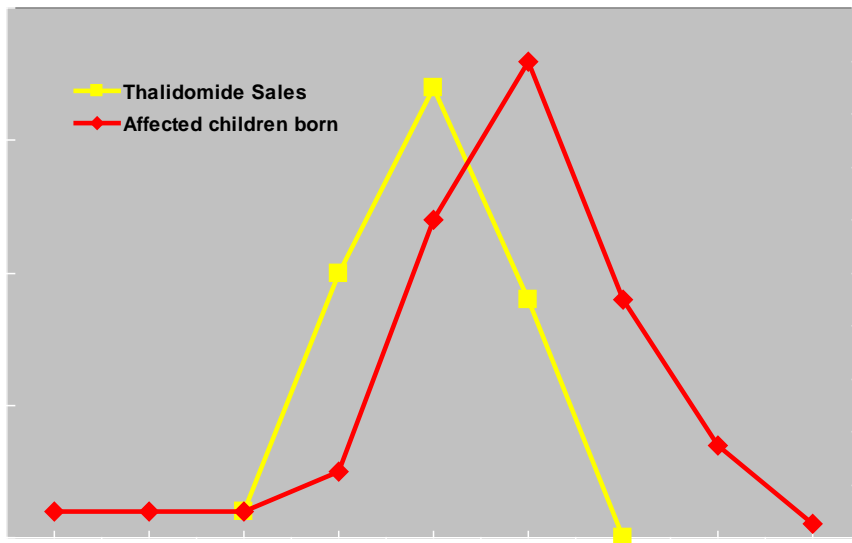
Thalidomide

- Developed by Grunenthal in 1950s
- Marketed as “completely safe” sedative
- Used for morning sickness
- Oral doses sometimes for first 4-5 months
- Primarily in Europe
- Relatively low toxicity based on animal studies
- US sales blocked by Dr. Francis O. Kelsey (US FDA) in fall 1960



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Thalidomide–Germany



Phocomelia:

Background 0.17/1000 live births

Post-drug 0.70/1000 live births

Thalidomide Today

- Thalidomide and Leprosy
- Brazilian Outbreak
- Sharing Drugs
- Belief that Thalidomide is preventive
- Repeat of 1960s?

Diethylstilbestrol (DES)

- Synthesized 1936 – Defined as 1st non-steroidal estrogen
- Treatment for threatened miscarriage from 1941-1971
- Low Estradiol Hypothesis (1940) drives usage
- Placental progesterone maintains pregnancy (late 1960s)
- Vaginal cancer in female offspring of DES moms
- *Herbst & Scully 1970*
 - *No good animal model until 1980s*

DES Lesions

- Female offspring of DES-treated mothers developed clear-cell adenocarcinoma of the vagina shortly after the onset of the menarchy (15-25 yoa) [FOAD]
- Higher incidence of miscarriages & malformed uteri
- Critical period of maternal exposure : 1st-trimester; development of urogenital ridge*
- Estradiol sensitive adenomatous tissues in the vagina
- Incidence in DES-daughters: 1-1.5/1000
- Male offspring? hydrocoele, hypospadias, cryptorchidism

Lessons Learned

- The placenta IS NOT a complete barrier
- Fetal susceptibility is gestational stage dependent
- Fetal susceptibility can be maternally determined
- Multiple forms of xenobiotics are teratogenic
- In utero toxicity can be manifested 1) at birth; 2) shortly after birth; 3) delayed until puberty; 4) several decades after birth
- In utero toxicity may occur in F2+n generations

Reproductive Toxicology 1960-PRESENT

- Thalidomide and DES disasters led to the rapid growth of reproductive toxicology and teratology, & a greater understanding of fetal biology & Fetal Origin of Adult Disease (**FOAD**) Barker, 1990 (**Epigenetics!**)
- New International Regulations for Reproductive Tests
- Thalidomide use today “déjà vu all over again”
- DES use today

Xenobiotics – Friends and Foes

- Environment
- Chemotherapeutics
- OTC drugs
- Lifestyle
- Sunlight/ Sound
- Foods/Supplements
- Today's Food Supplements

“The true science and study of
man is man himself”

Pierre Charron 1541-1603

Are *in vitro* and/or *in vivo* animal studies
enough?

Toxicology is not a mosaic. It is not modular nor is it predetermined. Rather, **Toxicology is continuous, interactive and emergent.**

That is our challenge!

“You too can be a Toxicologist in two easy lessons; each of 10 years”

Arnold Lehman