Learning from Bernardino Ramazzini

A tribute to the great master and to the Fellows of the Collegium Ramazzini
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The first textbook on occupational medicine:

*Liceat quoque interrogationem hanc adiicere, & quam artem exerceat –*

I may venture to add one more question: what occupation does he follow?
Ramazzini’s logic

1) Evaluate the EVIDENCE

2) Modify after LEARNING from victims:
   "I for one have done all that lay in my power, and have not thought it beneath me to step into workshops of the meaner sort now and again and study the obscure operations of mechanical arts."

3) And take prudent ACTION:
   “...to secure good conditions for workers... the art of medicine should contribute its portion for the benefit and relief... [We] ought to show peculiar zeal...in taking precautions for their safety.

It is better to prevent than to cure...”
“Longe praestantium est praeservare quam curare”

Bernardino Ramazzini (1633-1714)
On mercury poisoning in mirror-makers, Bernardino Ramazzini wrote:

“...these workers glower at the reflection of their suffering in the very mirrors they have made with their own hands and curse the profession they have had to follow.”

Der Spiegler, by Christoph Weigel (1698)
Evidence informed by
...learning from victims
as basis for prudent action

... using mercury as a paradigm
Focal

Widespread

Diffuse

FIG 1: Comparison of the distribution of lesions among the adult (A), non-fetal infant (B), and fetal infantile (C) Minamata disease. Takesuchi (67), with permission.

Learning from Minamata:

...in every case the mother was healthy, and it was not until more than three months after birth that the symptoms were recognized.

Shoji Kitamura (1959)
Key questions after Minamata

• Can methylmercury also at lower doses cause damage to the developing brain?
• ...and does it occur from environmental exposures far from local point sources?
• How polluted is the global environment?
• Is developmental neurotoxicity a general concern beyond lead and ethanol?
Faroe Islands

• Homogeneous, western culture
• Total population - 48,000
• High participation rate in prospective studies
• Fishing community with high seafood intake
• Wide range of exposures from traditional food (pilot whale)
Mercury toxicity at age 7 years expressed as *delay* in development (months) for a *doubling of the prenatal exposure*

Motor (Finger tapping, preferred hand) 0.9  
Attention (CPT-reaction time) 1.3  
Visuospatial (Bender errors) 0.6  
Language (Boston Naming) 1.6  
Verbal memory (CVLT short delay) 2.0

*(Average effect ~10% of s.d. or ~1.5 IQ points)*

(Grandjean et al., NTT, 1997)
Objective measure: Speed of electrical signals in the brain

Prolonged III-V interval on brainstem auditory evoked potentials at recent exposure in 14-yr-old children

(Murata et al., Journal of Pediatrics, 2004)
Modern imagining methods show that children with high prenatal pollutant exposure must activate brain regions not needed by controls.

Finger tapping with the left hand activates motor cortex on right AND left.

Increased prenatal exposure to MeHg (N = 3):

In non-exposed controls, only the right motor cortex is activated.

Controls (N = 3): (Roberta F.White et al., 2011)
Initial dissemination problems

- Our 1997 manuscript was rejected by three journals.
- When finally considered by a specialty journal (Neurotoxicol Teratol), major revision was requested several times.
- Right after publication, the article was criticized in Science.
- Today, this paper is by far the most highly cited in NTT since the journal’s inception.
Academic response: from skepticism to inertia

- White House review (1998): “…there are inadequate data on this to draw meaningful conclusions at this time”
- U.S. NRC (2000): EPA limit should be based on the Faroes study
- Hedged language remains: maybe, perhaps
- Pyrrhic victory: PubMed today lists almost 5,000 publications under the MeSH ”methyl mercury compounds”
Failure to recognize underestimated risk

- *Imprecise exposure assessment* causes bias toward the null
- *Covariate adjustment* can worsen this bias
- Seafood nutrients cause *negative confounding*
- *Cord blood* contains higher concentrations than maternal blood
- Early outcome assessments are *insensitive*
- Average effect hides *genetic predisposition*
Mercury’s environmental profile explored through polar bear hair

Polar bear hair from the Qilakitsoq interment in Greenland (about 1300 A.D.) had a mercury concentration of 0.52 µg/g.

Total enrichment of mercury since preindustrial times: ~10x

(Dietz et al., 2006)
Corporate response

• The tuna industry funded a campaign ("FishScam" and "MercuryFacts") for $25 million

• “In the United States, even the most rabid environmentalist cannot point to one sickened child or doddering old fool made ill from mercury”

• Hearing in the energy committee of the U.S. Congress: testimony by EPRI (2004)

• Conclusion by a medical colleague supported by EPRI: “Some people are convinced that mercury causes these effects and others are not so confident”
Concerned About Mercury?

You shouldn’t be. Unless you eat this.

Environmental scares about trace amounts of mercury in fish rely on a study of island snails that eat huge amounts of whole fish. However, scientists who study heavy metals find the health risks from mercury to humans you’re munching on a lovely fish sandwich, there’s no reason to worry.

Fish is good for you. Baseline anxiety (or whale blubber) isn’t.

mercuryfacts.org
“Doubt is our product”

(Brown and Williamson, 1969)

Quote from Glantz SA et al. The cigarette papers, UC Press, 1996

Are scientists innocent?
An idea that is not dangerous is unworthy of being called an idea at all

Oscar Wilde (1890) in ‘The Critic as an Artist’
Always remember that the numbers in your tables represent human destinies, although the tears have been wiped away.
Tough to be a victim

• First poisoning victim treated with calomel
• Exposed workers called “hysterical”
• One worker treated with electroshock
• Cause of Minatama disease disputed
• Iraqi Kurds poisoned by tainted grain
• Methylmercury use as fungicide banned only when export of eggs was threatened
• Current environmental mercury contamination will remain for decades
Silent pandemic

Number affected

Subclinical effects in child populations

Neurotoxicity in adults

Poisoning incidents

Time of recognition

(Grandjean & Landrigan, The Lancet, 2006)
Known neurotoxic to humans during development, N = 12

Neurotoxic to humans

N = 214

Neurotoxic in lab tests

N > 1,000

Chemical universe

N ~ 100,000

(Grandjean & Landrigan, 2006; 2014)
Has the fetus become the unfortunate miners’ canary for human exposure to toxicants in the environment?

Barry L. Johnson (1997)
Developmental Origins of Health and Disease (DOHAD):

Developmental stressors can lead to disease throughout life

Gestation | Childhood | Puberty | Reproductive life | Middle life | Later life

Environmental Exposures

Courtesy: NIEHS
Early development is the most important time for prevention of noncommunicable disease

Timely intervention produces substantial risk reduction

Impact of adult intervention is small

Fixed genetic contribution to risk is small

Mark Hanson, and Peter Gluckman Am J Clin Nutr 2011;94:1754S-1758S

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In Patavino Gymnasio Praticæ Medicæ Professoris Primarii,

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PRINCIPUM VALETUDINE
TUENDA
COMMENTATIO.

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TRAJECTI AD RHEUM,
Apud ABRAHAMUM & THIEL,
1712.
The public well-being depends wholly of the health of princes; it follows from this that nothing must be left untried to safeguard it.
Avoid underestimation of risks

• *Imprecise exposure assessment* causes bias toward the null and should be adjusted for

• *Covariate adjustment* must be carefully planned as it can worsen the bias

• Take into account *negative confounding*

• Outcome assessments must be *sensitive*

• Average effect may be misleading if *genetic predisposition* is present
Modern research-informed policy

Negotiation of Policy Options

Translation into Evidence-Informed Policy

Adjusted Priority Issues

Plan and Conduct Research

Consideration of Policy Implications

Research Outputs

Application of the "Precautionary Principle"
Brains Needed for the Future

Toxic chemicals damage brain development.

Fewer smart people are available to create safer chemicals.

World Environmental Health Day 2015

https://ourhealthandenvironment.wordpress.com/
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GENERATIO PROXIMO VALETUDINE TUEDA COMMENTATIO.

Accessit præter Indicem Rerum;
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TRAJECTI ad RHENUM,
Apud Abrahamum & Thiel, 1712.