

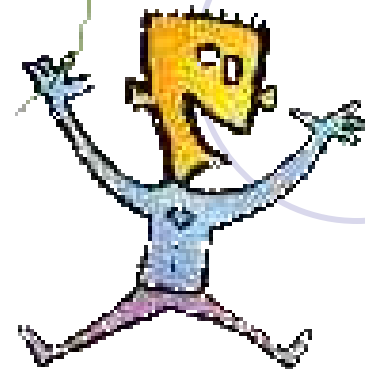
From toxicology to epidemiology: The example of lead

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Poisoning and Toxicity



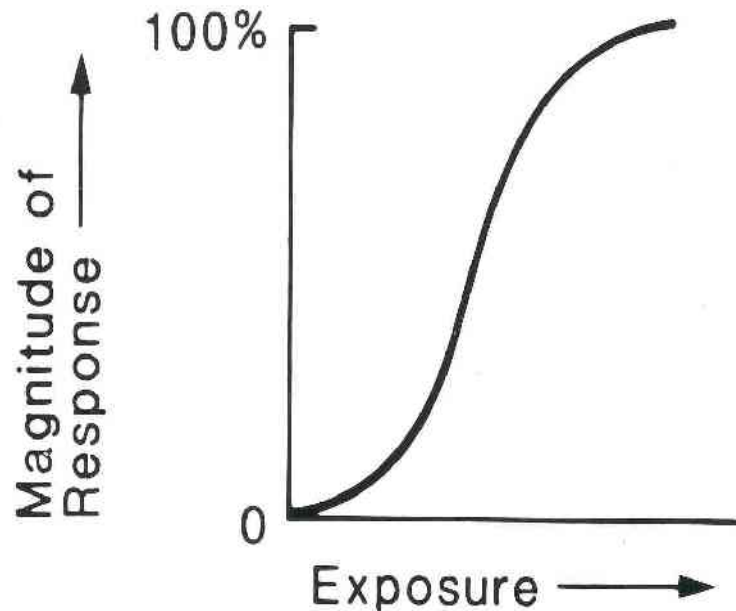
- Definitions are clear to a toxicologist
- Poisonings are cases
 - symptoms in a defined pattern (“toxidrome”)
 - corresponding to toxic effects
 - at a mid- to high level of exposure
- Toxicity
 - includes poisoning but refers to a broader spectrum of effects:
 - at the lower levels of exposure child may still be affected subclinically and in a multifactoral model

Multifactoral contribution

Subclinical

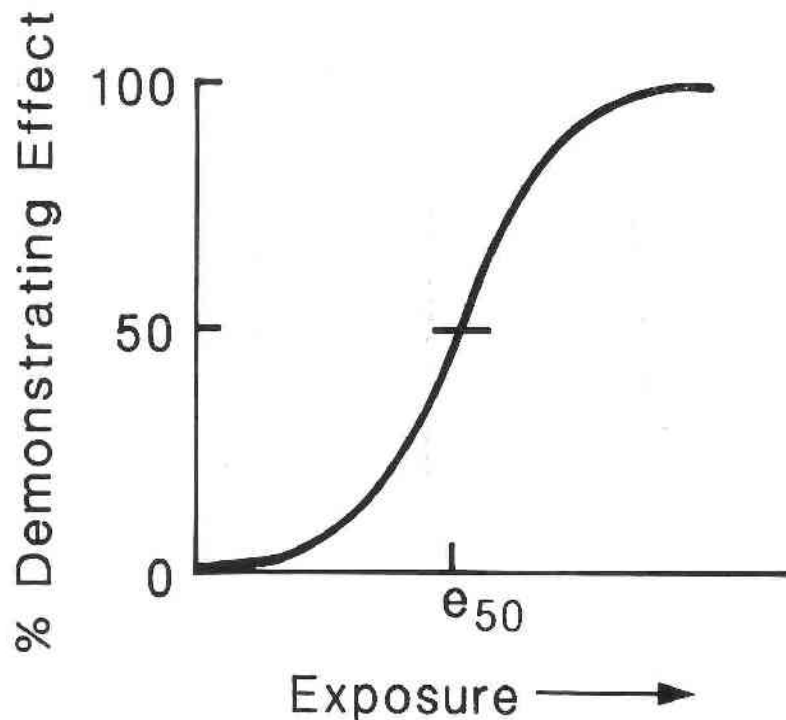
Poisoning

The Toxicological Exposure-Response Relationship



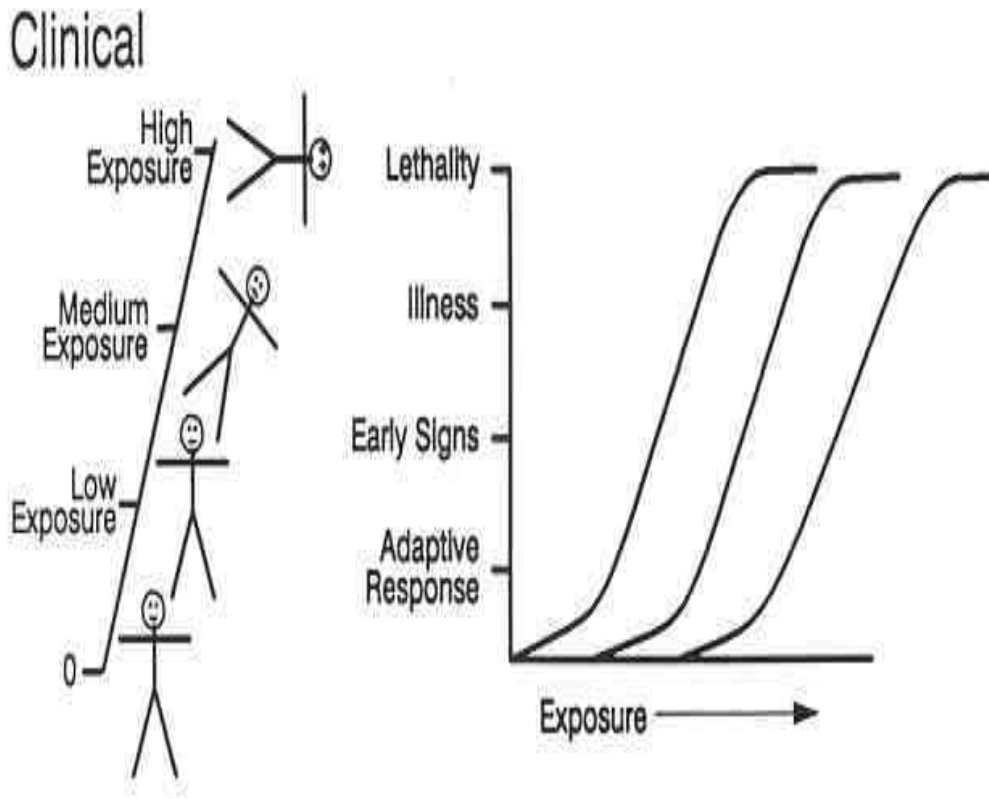
- Increasing exposure leads to increasing effect.
- Sigmoid (S) shape is characteristic.
- Evolving toxicity is “subclinical” or hidden until it reaches a level of detectability

The Epidemiological Exposure-Response Relationship



- Epidemiologists use the term a little differently.
- They are referring to increasing *numbers* of cases with increasing exposure.

Summary: Subclinical to clinical transition exposure-response relationship



- Increasing exposure leads to new symptoms, signs, additional manifestations of toxicity.
- Looks like a “stepladder” of signs and symptoms of toxic exposure.
- Useful clinically.

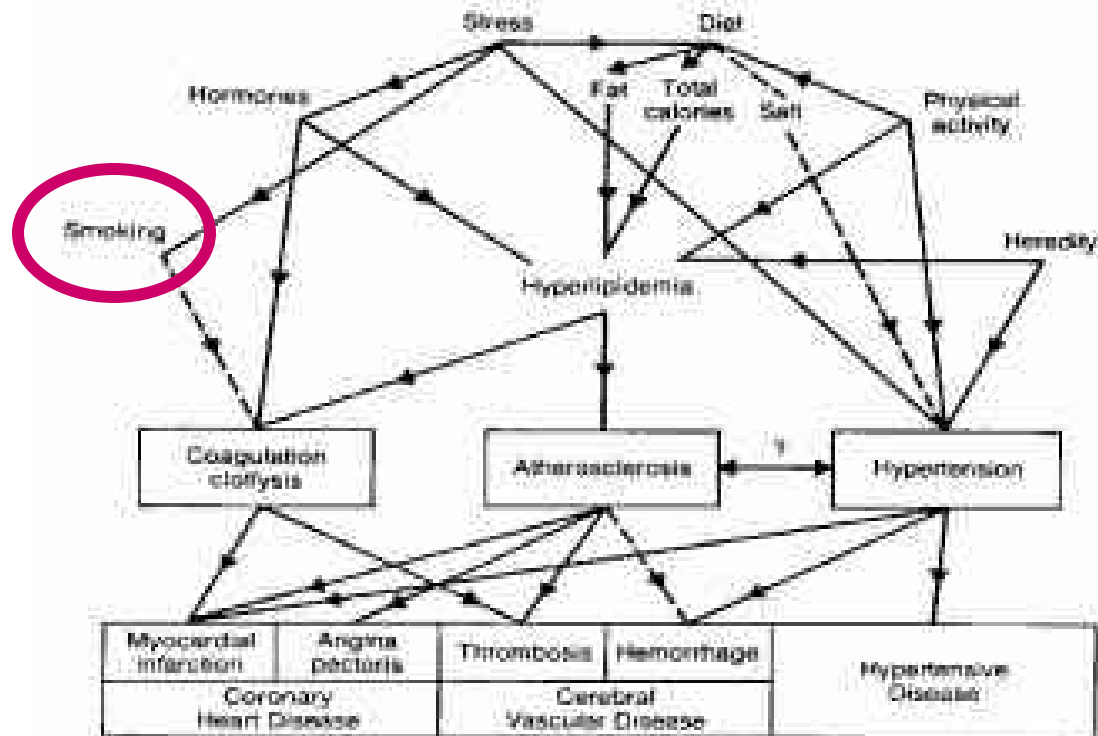


Toxicity as Risk Factor

- At low levels of exposure, exposure is risk factor in the epidemiological sense
 - of increasing the probability of a given outcome
 - without being the single determinant cause
- Question is what *drives* risk
 - For poisonings, exposure is only significant determinant
 - For subclinical toxicity, there is often an interaction with other factors, susceptibilities
 - For multifactorial models, not so clear

Multifactoral Disease Models

Web of Causation for the Major Cardiovascular Diseases



Web of Causation for the Major Cardiovascular Diseases. (Source: Stallones, R.A. (1966). Prospective epidemiologic studies of cerebrovascular disease. *Public Health Monograph No. 76*, Washington, DC: U.S. Government Printing Office. p. 53.)

Cigarette smoking as an example

Adults (active smoking)

- Acute “poisoning” (rare)
- Drives risk for lung disease
- Major risk factor for heart disease
- Also risk factors for heart disease:
 - Age and sex
 - Cholesterol, lipids
 - Heredity, hypertension
 - Cardiovascular fitness
 - Obesity
 - Stress
 - Many more

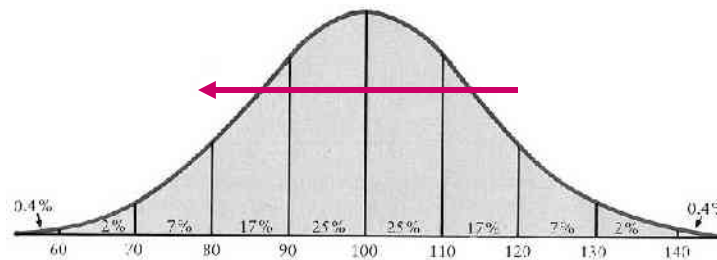
Children (passive smoking)

- CV disease not relevant
- Major trigger for asthma
 - Does not drive risk for incident asthma
- Drives risk (?) for
 - Bronchitis
 - Pneumonia
- Risk factor for multifactoral outcomes
 - Otitis media (multifactoral)
 - Low lung volume as adult
- Also risk factors for above:
 - Many other risk factors for each

Examples

Example: Neurobehavioral Effects of Lead

- **Lowers cognitive ability**
 - Reduced IQ, measures of academic performance
 - Individual impact small, subclinical
 - Population impact very significant
- Increased frequency of aggressive behavior
- Possible association with schizophrenia
- Animal studies suggest multifactorial effects

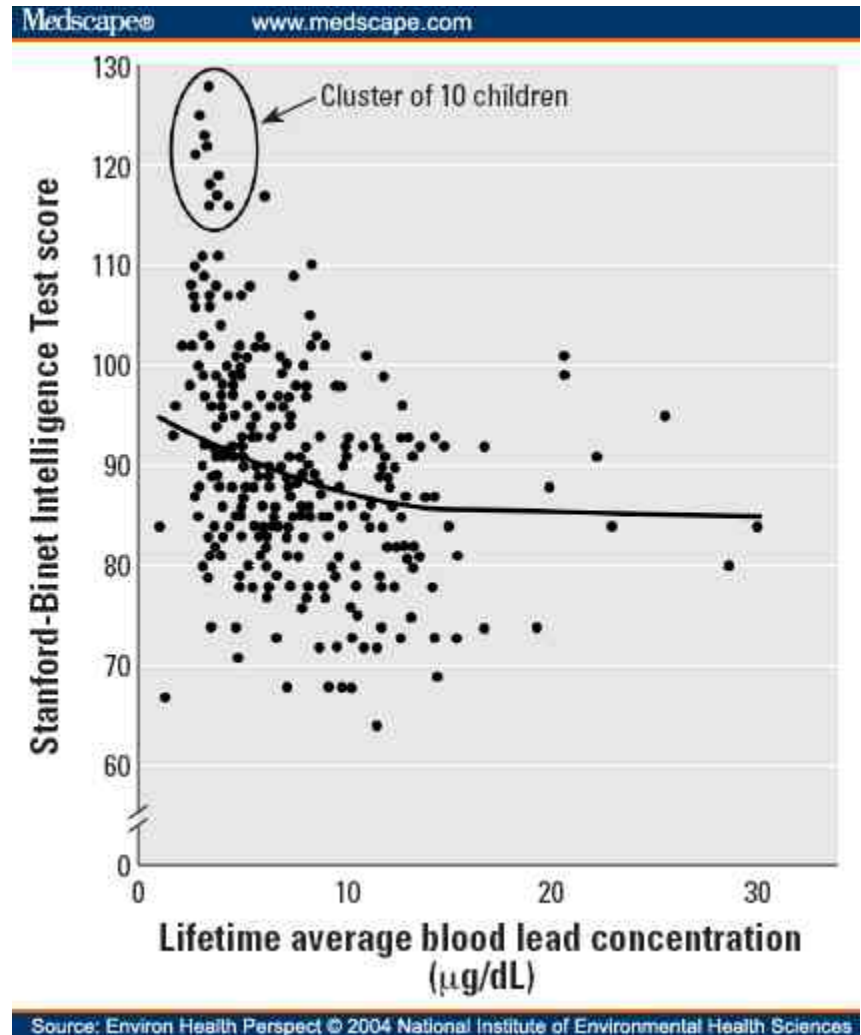


Subclinical Effects

Example: Lead toxicity

Lead exposure in children

- Acute poisoning occurs
 - Frequency driven by probability of encountering lead paint
- Subclinical toxicity (far left)
- Risk factor for multifactorial outcomes (near left)
 - Driven by cumulative lead intake from all sources
- Also risk factors:
 - Arsenic, mercury, endocrine disruptors (thyroid hormone mimics), inadequate omega fatty acid intake, inadequate early child stimulation, many others





Example: Washington, DC

Population of children:

<72 mo of age ~36,500

Mean (geom) blood lead level in 2005:

2.3 $\mu\text{g}/\text{dL}$ (v. 1.6 for USA), declining over time

Children with elevated BLL, 1998 - 2001:

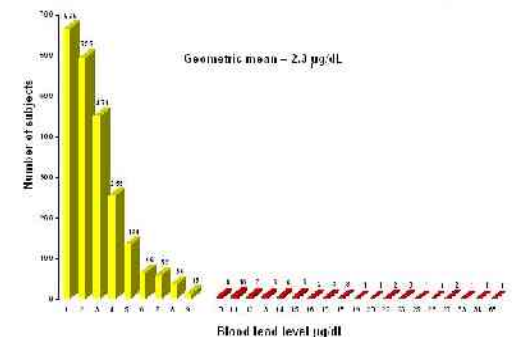
(> CDC level of concern: 10 $\mu\text{g}/\text{dL}$)

~ 250/year (about 4%), range 235 to 305,
relatively constant

(New York showed big drop during same
period)

What is (not) happening in Washington, DC?

- Mean levels continue to fall.
- Incidence of elevated BLL hardly changing in recent years.
- Why the discrepancy?
- Because the conditions have different *drivers*:
 - Elevated BLL by CDC: lead paint
 - GMean blood Pb: all source exposure, inc. soil lead
- Historically, driving factors were not closely linked
 - Lead paint ban: reduction in lead poisoning cases
 - Gasoline unleaded: reduction in mean lead levels



Implications

- Population v. individual effects
- Different drivers require different strategies:
 - To prevent individual “poisonings” (elevated BLL by CDC):
 - Track as frequency of elevated BLL
 - Reduce encounters with lead paint
 - To reduce population impact (multifactoral outcome):
 - Track by mean lead level
 - Reduce all-source exposure
 - Competition with other public health goals, however
- Lead risk to children is not a single problem.
- Requires different strategies.
- Topic for tomorrow!

Fig. 1. Dose-effect relationships for adverse health effects of lead exposure. (Adapted from ref. 24, with updating) ALA-U = δ -aminolevulinic acid in urine; CP-U = coproporphyrin in urine; NCV = nerve conduction velocity; CNS = central nervous system

