In Bed With The Devil: Recognizing Human Teratogenic Exposures

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In Bed With The Devil

- The only way we ever know that an exposure is teratogenic *in humans* is to recognize that it causes birth defects in babies.

Bradford-Hill Criteria

- Strength (effect size)
- Consistency (reproducibility)
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy
Bradford-Hill Criteria

• Generally accepted (with some elaboration and caveats) for establishing causality in humans on the basis of multiple high-quality epidemiology studies
• Rarely used in teratology

Bradford-Hill Criteria

• Would require hundreds to thousands of babies to be born with birth defects before causality established
• Ignores the evidence of teratogenicity in humans that is usually most compelling
The Smoking Gun

- Congenital Rubella Syndrome
- Thalidomide Embryopathy
- Fetal Alcohol Syndrome
- Congenital Zika Virus Syndrome

The best way to recognize teratogenic patterns of congenital anomalies is examination by a skilled physician

- Does not scale easily
In Bed With The Devil

- Our challenge is to recognize this quickly and efficiently, when the fewest possible babies have been harmed.

Recognizing Teratogenic Exposures in Humans

1. Babies who have been harmed by the exposure.
2. A way to associate the exposure to the babies’ birth defects.
3. A way to prove that the observed association is causal.
Recognizing Teratogenic Exposures in Humans

- Experimental studies - may be supportive, but never necessary or sufficient
- Case reports, clinical series
- Epidemiology studies
- Other considerations

Case Reports and Clinical Series

- Alert clinicians: Where recognition of most important human teratogenic exposures starts
- Permit recognition of characteristic patterns of anomalies (syndromes)
Case Reports and Clinical Series

- High sensitivity, poor specificity
- Useful for raising causal hypotheses, but most are wrong
- Neither necessary nor sufficient, but the best means of surveillance we have

Epidemiology Studies

- Only reliable way to obtain quantitative estimate of risk and statistical significance associated with a human teratogenic exposure
Randomized Controlled Trials

• Provide most reliable risk estimates
• Rarely used for human teratology
• Pregnancy itself may be treated as an adverse outcome
• Birth outcome data usually of poor quality

Cohort Studies

• Compare frequency of birth defects among children born to women treated (or not) with an agent during pregnancy
• Directly address the question that most pregnant women have about an exposure
Cohort Studies

- Population-based
  - Very large (very expensive)
- Exposure cohort
  - Usually identified through a pregnancy registry or calls to a teratogen information service
  - Not population-based

Cohort Studies

- Require large numbers of exposures/birth defect outcomes
- Quality of birth defect outcome data is often an issue
- Confounding or effect modification may be concerns
Case-Control Studies

- Compare frequency of maternal treatment during pregnancy among children with or without birth defects

Case-Control Studies

- Can only be used to look for association with birth defects present in cases
- Statistical significance often not the same as clinical significance
**Case-Control Studies**

- Require large numbers of birth defect outcomes/exposures
- Quality of exposure data is often an issue
- Confounding or effect modification may be concerns

**Record Linkage Studies**

- Performed by linkage of existing administrative, vital statistics and/or registry data
- May use cohort, case-control or hybrid design
- Data sets often large
- Cost-effective
Record Linkage Studies

- If data are collected for another purpose (e.g., billing), quality often limited for teratology studies
- Information on potential confounders or effect modifiers is often unavailable

Ecological Studies

- Test for association between summary measure of exposure and a summary measure of disease in a group
- Often done with data collected for other purposes
- Cost effective
Thalidomide and Thalidomide Embryopathy


Ecological Studies

Autism
Organic Food Sales

$r=0.9971$ ($p=0.0001$)
Registries

• With appropriate internal control: exposure cohort study
• Without appropriate internal control: case series, often with less consistent data collection

Registries

• May (or may not) permit recognition of recurrent patterns of malformations
• Confounding or effect modification often concerns
• Statistical analysis may be inappropriate
Recognizing Teratogenic Exposures in Humans

• How can we “prove” an exposure is teratogenic without definitive studies?

Recognizing Teratogenic Exposures in Humans

• Let the computer do it
• Formal meta-analysis
• Expert consensus
Let The Computer Do It

- Algorithm, machine learning, neural networks, etc.
- Currently risks violating the First Law of Robotics

Recognizing Teratogenic Exposures in Humans

- Let the computer do it
- Formal meta-analysis
- Expert consensus
Formal Meta-analysis

• Systematic approach to identifying, evaluating, synthesizing and combining the results of relevant studies in a particular area

• Useful when there are multiple studies, each with limited power
• May permit quantitative conclusions to emerge that cannot be drawn from individual studies
• Can assess effects of biases and limitations of individual studies
Formal Meta-analysis

- Useless when there are very few or no studies
- May be misleading
  - Garbage in, garbage out
  - Mixing apples and oranges
  - The file drawer problem

Formal Meta-analysis

“Statistical alchemy for the 21st century”

...Alvan Feinstein
Recognizing Teratogenic Exposures in Humans

- Let the computer do it
- Formal meta-analysis
- Expert consensus

Expert Consensus

- Can simultaneously evaluate studies of different types, sizes, and quality, including non-epidemiological studies
Expert Consensus

- Consensus is qualitative, not rigorously quantitative
- Time-intensive, requires real expertise = Expensive
- Value of consensus depends on who is making it

Expert Consensus

- Process is subjective but must be seen as authoritative
- Consensus is always provisional and subject to change on the basis of new or better information
- Consensus must be reviewed/renewed periodically
Expert Consensus

- All relevant data that are available must be considered.
- Evidence should be evaluated and weighted by data quality, consistency and relevance.
- The assessment should be made in the context of likely exposures.

Expert Consensus

- Shepard’s Criteria can provide a useful framework for this evaluation
  - Not an algorithm
  - Cannot be applied without expert assessment of each point
Shepard’s Criteria (2010)

1. Proven exposure to the agent at critical time(s) in development
2. Consistent findings by ≥2 high-quality epidemiological studies
3. Careful delineation of clinical cases
4. Rare environmental exposure associated with rare defect

Shepard’s Criteria (2010)

5. Teratogenicity in experimental animals
6. The association should make biological sense.
7. Proof that the agent acts in an unaltered state in an experimental system
Zika Virus and Birth Defects — Reviewing the Evidence for Causality

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“We conclude that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies”

Zika Virus Example

• From first clinical observations to inference of causality as a human teratogen in <1 year
• Subsequent studies support conclusion of causality
• Statement motivated research and public health activity in this area

Zika Virus Example

• Why was this successful?
  - Alert clinicians recognized something unusual
  - Public health officials listened and investigated quickly
  - Necessary expertise, resources and infrastructure available
Zika Virus Example

• Why was this successful?
  - Required expertise, resources and infrastructure deployed quickly and efficiently
  - Strong and effective leadership for response

Is This Cheating?

Maybe

• It is the right thing to do.
• Our conclusions must always be provisional, subject to change if better information becomes available.
Could you or I (or CDC) do as well next time?

What We Need

• More and better surveillance (hypothesis generation):
  - Case reports and case series
  - Registry studies
  - Epidemiology studies
What We Need

• More and better targeted hypothesis testing studies:
  - Epidemiology studies
  - Experimental teratology studies
  - Basic science studies of normal and abnormal embryonic development

What We Need

• Ways to collect and analyse available data quickly and effectively
• Ways to target and implement hypothesis testing studies quickly and effectively
What We Need

- Commitment
- Funding for infrastructure and rapid response
- Positive incentives for doing what is right

Babies are being harmed unnecessarily!