BE.104 Spring
Environetics; Cause and Effect
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Outline

I. Environetics
II. Cause-Effect Determination

I. ENVIRONETICS

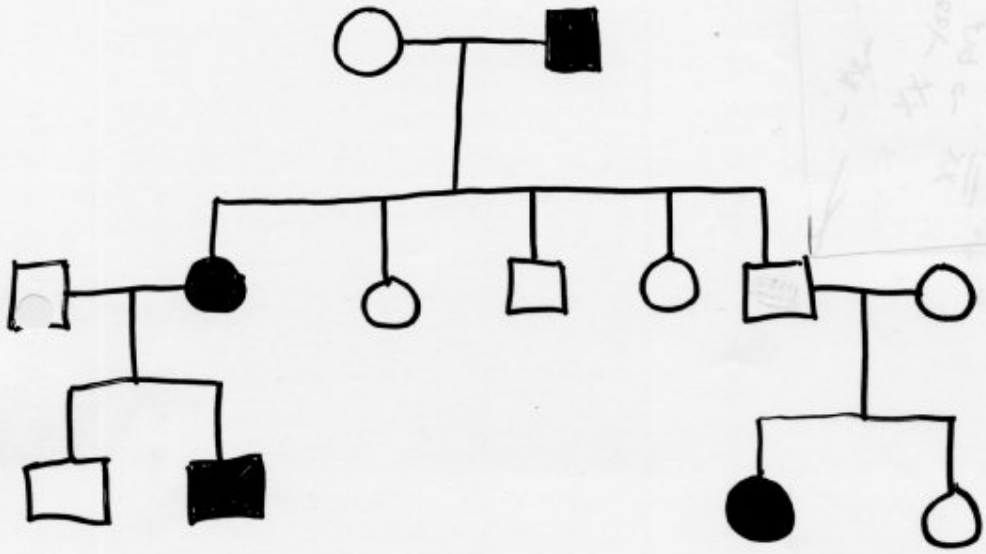
Definition: Environetics is that discipline that seeks to detect and quantify cause-effect relationships between non-infectious environmental agents and human health.

Environetics employs concepts from epidemiology, biostatistics, logic, and good ol' common sense to make this determination.

For perspective, consider "The Genetic Paradigm of Disease"

Figure 1A:

Genetics



(Chance)

1A

"All diseases are genetic." Not necessarily "hereditary," but caused by defects in genes.

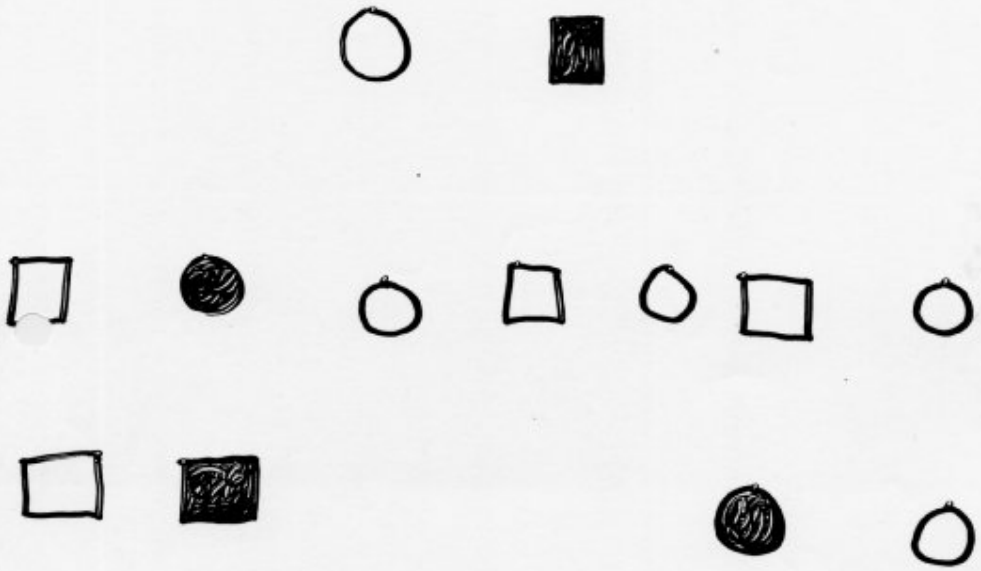
Refinement: All diseases are genetic except for those caused by toxins and infectious agents, which may also have dependencies on genotype (e.g., susceptibility)

Genetics- Currently this discipline is out of control vs. environmental mechanisms

Are all diseases due to defects in genes?

Figure 5A:

Environetics



CHANCE

5A

Genetic Pedigree Analysis

The gold standard for analysis of genetic disease factors

Discover genetic disease causation (i.e. gene) by:

1) Relating disease patterns to genetic rules $\Rightarrow$

Genotype classification

a) dominant
b) recessive
c) x-linked
d) age-dependent (e.g. childhood cancers)

2) "Quantitative relating" is called linking,

a statistical method for detecting and quantifying the significance of associations between genotype and disease occurrence (e.g., genotyping across $3x10^9$ bp!; mutation analyses; LOD score)

3) Establishing cause-effect:

strength of association
prospective analysis (genotype before disease)
animal models (some limitations)

Genetics Features

Rules

1) gene → product (protein, ribonucleic acid) → function for health
2) Mendelian segregation- 1884

Confounders of the Analysis

1) Penetrance ("mutation expressivity")
2) Imprinting- specific subset of penetrance (mechanism known)
3) Phenocopy - (phenotype for other reasons besides the gene of origin)
4) Ascertainment (e.g., determining familial relationship)
5) "Environment effects"
6) Statistical variation? Yes, spontaneous mutations (sporadic cases)

Statistics requirements- n is small

Key Research Tool- Old - Linkage analysis (stat. associations)
New - Genomics: How genes are **expressed**
⇒"quantitative gene expression pedigrees" may be next

Experimental Support- Mouse models-Disease synteny
Transgenic KO's
Human analyses-
Human hereditary disease w/genotyping

Societal benefits- Advances in clinical medicine

Environetics

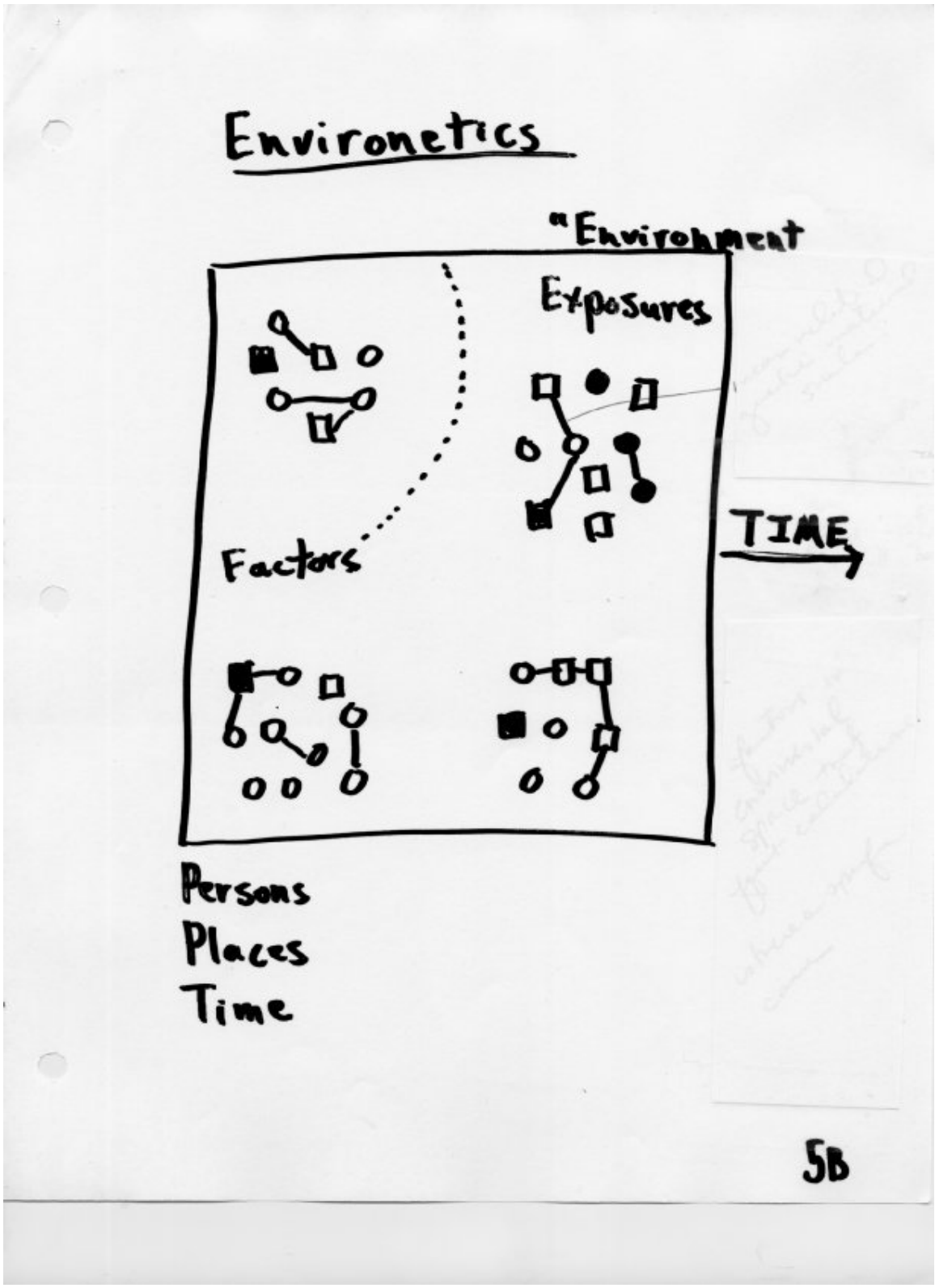


Figure 5B: persons, exposures, geographical space, time

The component that genetics leave out

The **Environmental Health Science Study** or the **Public Health Study** as more commonly known
-the gold standard for detecting environmental health factors

Discover chemical disease etiology (i.e., "toxin") by:

1) Relating patterns of disease and toxicity to toxicology rules ⇒ toxicology classifications and principles of epidemiology; e.g.,

a) Acute
b) Chronic (and subchronic)
c) Clustered
d) Uniform Distribution
e) Age-dependency
f) Factor-dependency (e.g., workplace in vs outdoors)

2) "Quantitative relating" is Biostatistics, methods for detecting and quantifying the significance of associations between toxin exposure and health (e.g., retrospective studies, p-value, confidence limits, RR, AR, etc.)

3) Establishing cause-effect: Prospective Intervention studies
Humans - accidents
Animal models- limited relevance to human health

Environetics Features

Rules

Maimonides- 1198
Spanish physician & philosopher (Mendel, not until 1884)
"Poisons and Their Antidotes"- book published
"Earliest attempt to describe the field of toxicology"

1) Chemical → target (protein, gene, biochemical) → function for health
2) Dose ⇒ k(disease phenotype or toxicity); i.e., Dose-Response relationship

Confounders

1) (Resistance/Susceptibility) Sensitivity- general, many unknown & known causes
2) Barriers <Source & Transport>- agent-specific
3) "Toxocopy" - health effect for other reasons than suspected agent (e.g., endogenous causes for asthma)
4) Exposure (were they exposed or not?)
5) Genetic/Familial effects (clusters)
6) **Statistical variation and error! Major confounder**
7) Human psychology

Statistics requirements- n is large compared to genetic pedigree analyses

Key Research Tool-Epidemiology (associate disease w/ exposure)
On the horizon: Toxicogenomics- toxic expression profiles

Experimental Support- Rodent- Toxicology Evaluations
Human- Public Health Interventions, Accidents

Societal benefits- Regulations for Public Health

Populations at Risk are often special groups
(General)
Young
Old
Clinical
Workers

The Environetics Method

1) Design a study to look for an association
2) Confirm statistical significance
3) Perform orthogonal statistics-based study <ideally with NEW DATA SET>

Purpose:
Build scientific confidence & statistical confidence

4) **Ideal: Intervention Analysis- Critical for establishing Cause-Effect Relationship**

The intervention is the "laboratory experiment" of a public health study

5) Attempt to relate to toxicological mechanisms for greater scientific confidence

II. CAUSE-EFFECT RELATIONSHIP DETERMINATION

What we start with is an association:

agent X α disease or toxicity

(After first establishing a statistically significant association!)

We want to know:

Does **agent X cause the disease or toxicity**?

Often, the standard applied is "Preponderance of evidence" (the civil case); instead of "beyond a reasonable doubt" (the criminal case)

Why do we care to establish C-E (cause effect) relationship or to rule them out?

1) To intervene: control permits development of sound and effective public health policy

2) To predict future disease/toxicity occurrences

3) To prevent wasting resources on erroneous conclusions

4) To avoid litigation <Our chemicals are safe!>

5) To assign responsibility <Your chemicals are not safe!>

Ideally,

To define an absolute C-E Relationship, two conditions must be satisfied.

(*Absolute* means that an agent is solely responsible for an observed disease or toxicity. This is the most straightforward case to evaluate. Cases of multiple responsible agents are addressed in the following discussion).

If we say, "A is the cause of B", then

1) If A, then B
   I.e., A is sufficient for B

2) If not A, then not B
   I.e., A is necessary for B

"Necessary and sufficient"

Therefore, if we alter A, we will also alter B in a predictable fashion.

This is the **Ideal C-E Relationship** for effective intervention

This a **“Single Factor Mechanism”**

(We often face multi-factor systems)

***When** these are **true**, there **is** a C-E relationship; BUT, a C-E relationship could also exist in their absence, too!

The necessary-and-sufficient test is poor for sensitivity, but has great specificity. I.e., it may miss responsible factors if multiple factors can cause the disease or toxicity. However, it gives few false positives! If an agent meets this test, you will never conclude it is C-E related when it is not.

Common Confounders & Errors when "A alone causes B" is thought to be true.

1) Carcinogen Fatty Foods ⇒ ↑Absorption Liver Cancer

A (+ X) ⟶ B

A necessary, but not sufficient

Test needed to discover error:
Evaluate A vs B in different people ⇒
sometimes B, sometimes not B.
Only changing A, will mislead!

2) Carcinogen Liver Cancer

A ⟶ B

Dust Asthma Attack

&

HBV

(X ⟶) B

Exercise

("Riding bike down dusty road")

A is sufficient, but not necessary

Test needed to discover error:
{Remove A, B remains; ↑A, will mislead!}

3) (Bacteria) Fever Sepsis
(X) ⟶ A + B

Highly correlated,
but A neither necessary, nor sufficient for B

<u>Test needed to discover error:</u>
Remove A, B remains; ↑A, B unchanged; fails both tests

4) A:B Chance Association!
E.g. same location, same time, etc.

Not necessary, not sufficient

<u>Test needed to discover error:</u>
{Remove A, B remains; ↑A, B unchanged}

5) Artifactual- Errors in method
- Statistics
- Measures, instruments
- Fraud, competency

Two Common Questions for C-E Analysis

1) Most common: **Does A cause B?**
   Watch out for bias! Suspected

2) What X causes B?
   Unknown!

Summary of the Environetics Approach

1) Rule out genetic (look for familial relations)

2) Establish statistically significant relationships
    a) Retrospective typical
    b) Small "pilot" study

3) Apply scientific method
    a) Observe = statistical analyses
    b) Develop hypothesis
    c) Test hypothesis
        i. statistical predictions- NEW ONES
        Avoid just conducting a larger study
        (e.g., first before-after exposure study; next length of exposure study)
        ii. Intervention (dose effects)
        Necessary-sufficient
        "Koch's Postulates"

Henle-Koch's Postulates for Microbes versus Environetics

I. Find agent in all cases of disease <suggests necessary>
<For Environetics, this may mean detecting the agent, its byproducts, or metabolites, etc.>

II. Isolate from diseased individuals and grow in pure culture
<For Environetics: detect & identify and use pure chemical>

III. Cause disease is susceptible host
<proves sufficient; tough in people!>

IV. Re-isolate the agent from infected hosts with disease
<For Environetics, look for same byproducts or metabolites in new disease cases>

4) Prospective Public Health Study (also fits in 3c above)
With possibility of varying A "experimentally"

Consider a classic Public Health Study applying the Environetics Approach to an example of a beneficial chemical in the environment

1) 1930's
Recognized that fluoride in water supply was associated with increased prevalence of mottled enamel on teeth because of effects on dentin deposition

2) A dentist formed the impression that people with mottled teeth had fewer cavities:

NaF : ΔHealth?

3) The U. S. Public Health Service (PHS) conducted surveys with children 12-14 yrs old.

Fig 1-1 $\Rightarrow$ F is associated with positive ΔHealth (statistical analysis not shown!)

4) Intervention:
Conduct study with similar communities with low natural fluoride
Fluorinate some & not others
Evaluate ΔHealth at a later time (i.e., prospectively)

Table 1-1

If NaF, ΔHealth?	Sufficient (Newburgh)
Not NaF, Not ΔHealth	Necessary (Kingston)

"And the rest is Environetics history…"