The Epidemiologic Approach to Causation

HISTORICAL DEVELOPMENT OF THEORIES OF CAUSATION

- 1. Divine retribution; imbalance in body humors caused by air, water, land, stars; spontaneous generation

- 2. Miasma: Disease transmitted by miasmas or clouds clinging to earth's surface

HISTORICAL DEVELOPMENT OF THEORIES OF CAUSATION

- 3. Germ Theory of Disease and Henle-Koch Postulates:

- Most important postulate is that the microorganism must always be found with the disease. This postulate embodies the idea of specificity of a cause. That is, a one to one relationship between an exposure and a disease.

HISTORICAL DEVELOPMENT OF THEORIES OF CAUSATION

- 4. Web of Causation

- A paradigm for the causes of chronic diseases. Most important shift from Henle-Koch Postulates is the idea of multiple causes. Postulates were also revised for establishing causation in chronic diseases.

HISTORICAL DEVELOPMENT OF THEORIES OF CAUSATION

- 5. Recent Controversies
- Causation cannot be established. Causal criteria should be abandoned. Has anyone seen the spider that produced the web?

What is a Cause?

- Merriam-Webster Dictionary: Something that brings about a result especially a person or thing that is the agent of bringing something about.

- KJ Rothman: An event, condition, or characteristic without which the disease would not have occurred.

- M Susser: Something that makes a difference.

Problem: How do we know when something makes a difference?

Association is not equal to causation.

Consider the following statement: If the rooster crows at the break of dawn, then the rooster caused the sun to rise.

Characteristics of a cause

- 1. Must precede the effect (proximate vs. distant)

- 2. Can be either host or environmental factors (e.g., characteristics, conditions, actions of individuals, events, natural, social or economic phenomena)

- 3. Positive (presence of a causative exposure) or negative (lack of a preventive exposure)

- The term <u>risk factor</u> is often used to describe factors that are positively associated with the risk of development of a disease (but not sufficient to cause disease)
- Epidemiological studies can measure the relative contribution of each risk factor to disease occurrence
  - allows priority setting for disease control
  - possible to prevent disease by targetting one piece of the pie

Establishing the cause of disease

- Koch (1884) provided a framework for identifying causes of infectious disease

- Koch's postulates:

  - the agent has to be present in every case of the disease

  - the agent has to be isolated and grown in pure culture

  - the agent has to cause disease when inoculated into a susceptible animal and the agent must then be able to be recovered from that animal and identified

'Single cause' paradigm

Establishing the cause of disease

- Koch's postulates:
  - anthrax was the first disease demonstrated to meet these rules
  - really of value only when the specific cause is an overpowering infectious agent
- For many conditions (both infectious and non-infectious) Koch's postulates are inadequate:
  - e.g. MCD

GENERAL MODEL OF CAUSATION (CAUSAL PIES)
BY KJ ROTHMAN

- Sufficient cause:

- A set of conditions without any one of which the disease would not have occurred. (This is one whole pie.)

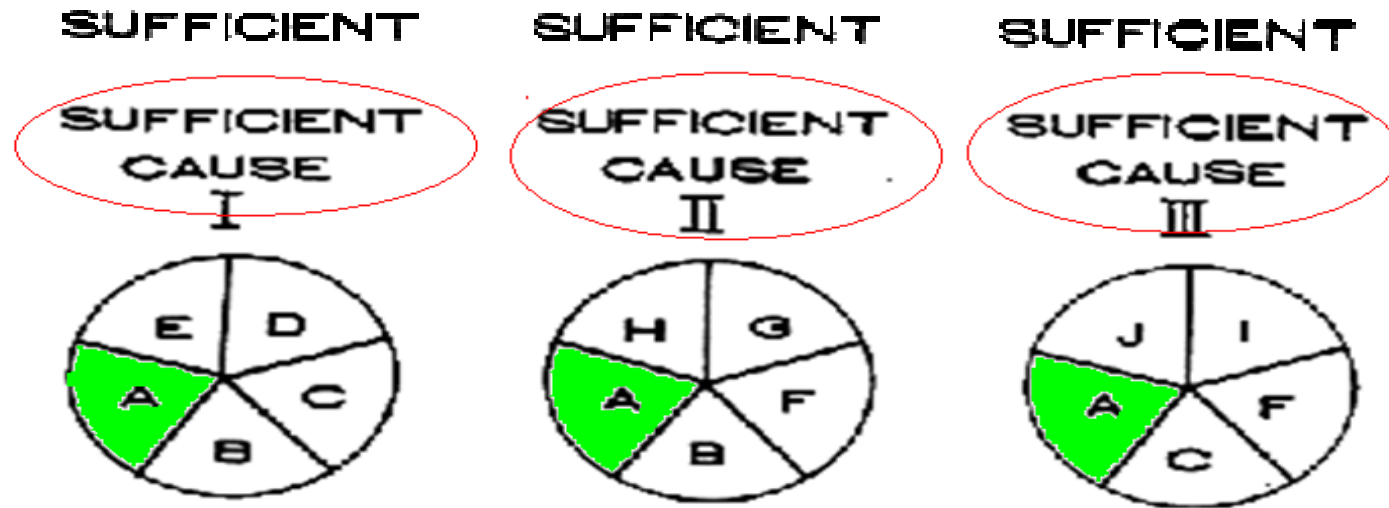# GENERAL MODEL OF CAUSATION (CAUSAL PIES)
BY KJ ROTHMAN

- Component cause:

- Any one of the set of conditions which are necessary for the completion of a sufficient cause. (This is a piece of the pie.)

GENERAL MODEL OF CAUSATION (CAUSAL PIES)
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- Necessary cause:

- A component cause that is a member of every sufficient cause.

GENERAL MODEL OF CAUSATION (CAUSAL PIES)

This illustration shows a disease that has 3 sufficient causal complexes, each having 5 component causes. A is a necessary cause since it appears as a member of each sufficient cause.
B, C, and F are not necessary causes since they fail to appear in all 3 sufficient causes.

Attributes of the causal pie

- 1. Completion of a sufficient cause is synonymous with occurrence (although not necessarily diagnosis) of disease.

- 2. Component causes can act far apart in time.

Attributes of the causal pie (cont'd)

- 3. A component cause can involve the presence of a causative exposure or the lack of a preventive exposure.

- 4. Blocking the action of any component cause prevents the completion of the sufficient cause and therefore prevents the disease by that pathway.

Factors in causation

- Predisposing: age, gender and previous illness create a state of high susceptibility

- Enabling: low income, poor nutrition, poor medical care favour development of disease Precipitating: exposure to noxious agent may be associated with onset of disease

- Reinforcing: repeated exposure to stress might aggravate established disease

Establishing the cause of disease

- Causal inference is the term used for the process of working out whether observed associations are likely to be causal

Establishing the cause of disease

- Recognising the shortcomings of Koch's postulates, epidemiologists in the 20th century required a more systematic approach to establishing cause and effect relationships
  - US Surgeon General (1964) used this approach to establish that cigarette smoking caused lung cancer
  - this approach further elaborated by Bradford Hill (1965) in a set of 'guidelines for causation'

Causal "guidelines" suggested by Sir AB Hill (1965)

- Temporality
- Plausibility/Coherence
- Consistency
- Strength of the association
- Biological gradient/Dose-response relationship
- Reversibility/Experiment
- Analogy/Study Design
- Specificity

Causal "guidelines" suggested by Sir AB Hill (1965)

Purpose: Guidelines to help determine if associations are causal. Should not be used as rigid criteria to be followed slavishly. Hill even stated that he did not intend for these "viewpoints" to be used as "hard and fast rules."

1. Temporality

- The causal factor must precede the disease in time.

- This is the only one of Hill's criteria that everyone agrees with.

1. Temporality (cont'd)

- Prospective studies do a good job establishing the correct temporal relationship between an exposure and a disease.

- Example: A prospective cohort study of smokers and non-smokers starts with the two groups when they are healthy and follows them to determine the occurrence of subsequent lung cancer.

2. Plausibility / Coherence

- Biological or social model exists to explain the association. Association does not conflict with current knowledge of natural history and biology of disease.

- Example: Cigarettes contain many carcinogenic substances.

2. Plausibility / Coherence

- Many epidemiologic studies have identified cause-effect relationships before biological mechanisms were identified. For example, the carcinogenic substances in cigarette smoke were discovered after the initial epidemiologic studies linking smoking to cancer.

3. Consistency

- The association is observed repeatedly in different persons, places, times, and circumstances.

- Replicating the association in different samples, with different study designs, and different investigators gives evidence of causation.

3. Consistency (cont'd)

- Example: Smoking has been associated with lung cancer in at least 29 retrospective and 7 prospective studies.

- Note: Sometimes there are good reasons why study results differ. For example, one study may have looked at low level exposures while another looked at high level exposures.

4. Strength of the association

- The larger the association, the more likely the exposure is causing the disease.

- Example: Relative risk of lung cancer in smokers vs. non-smokers = 9; Relative risk of lung cancer in heavy vs. non-smokers = 20

4. Strength of the association (cont'd)

- Strong associations are more likely to be causal because they are unlikely to be due entirely to bias and confounding.

- Weak associations may be causal but it is harder to rule out bias and confounding.

5. Biological Gradient/Dose-response relationship

- A "dose-response" relationship between exposure and disease. Persons who have increasingly higher exposure levels have increasingly higher risks of disease.

- Example: Lung cancer death rates rise with the number of cigarettes smoked.

- Some exposures might not have a "dose-response" effect but rather a "threshold effect" below which these are no adverse outcomes.

6. Experiment/Reversibility

- Investigator-initiated intervention that modifies the exposure through prevention, treatment, or removal should result in less disease.

- Example: Smoking cessation programs result in lower lung cancer rates.

- Provides strong evidence for causation, but most epidemiologic studies are observational.

7. Analogy/Study design

- Has a similar relationship been observed with another exposure and/ or disease?

- Is the evidence based on a strong study design

- Example: Effects of Thalidomide and Rubella on the fetus provide analogy for effects of similar substances on the fetus.

8. Specificity

- A single exposure should cause a single disease.

- This is a hold-over from the concepts of causation that were developed for infectious diseases. There are many exceptions to this.

8. Specificity (cont'd)

- Example: Smoking is associated with lung cancer as well as many other diseases. In addition, lung cancer results from smoking as well as other exposures.

- When present, specificity does provide evidence of causality, but its absence does not preclude causation.

Hill concludes...

- "Here then are nine different viewpoints from all of which we should study association before we cry causation.... None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or lesser strength, is to help us make up our minds on the fundamental question --is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

- We disagree with one part of this statement: Temporality is a sine qua non for causality.

In summary, Sir Bradford Hill's "guidelines" are useful guides for:

- **Remembering distinctions between association and causation in epidemiologic research;**

- **Critically reading epidemiologic studies;**

- **Designing epidemiologic studies;**

- **Interpreting the results of your own study.**