

Association & Causation

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Suggest an etiological hypothesis



Analytical & experimental studies



Test the hypothesis derived for observed **RELATIONSHIP** b/w suspected cause & disease

ASSOCIATION

- ▶ **Definition:** the concurrence of two variables more often than would be expected by chance.

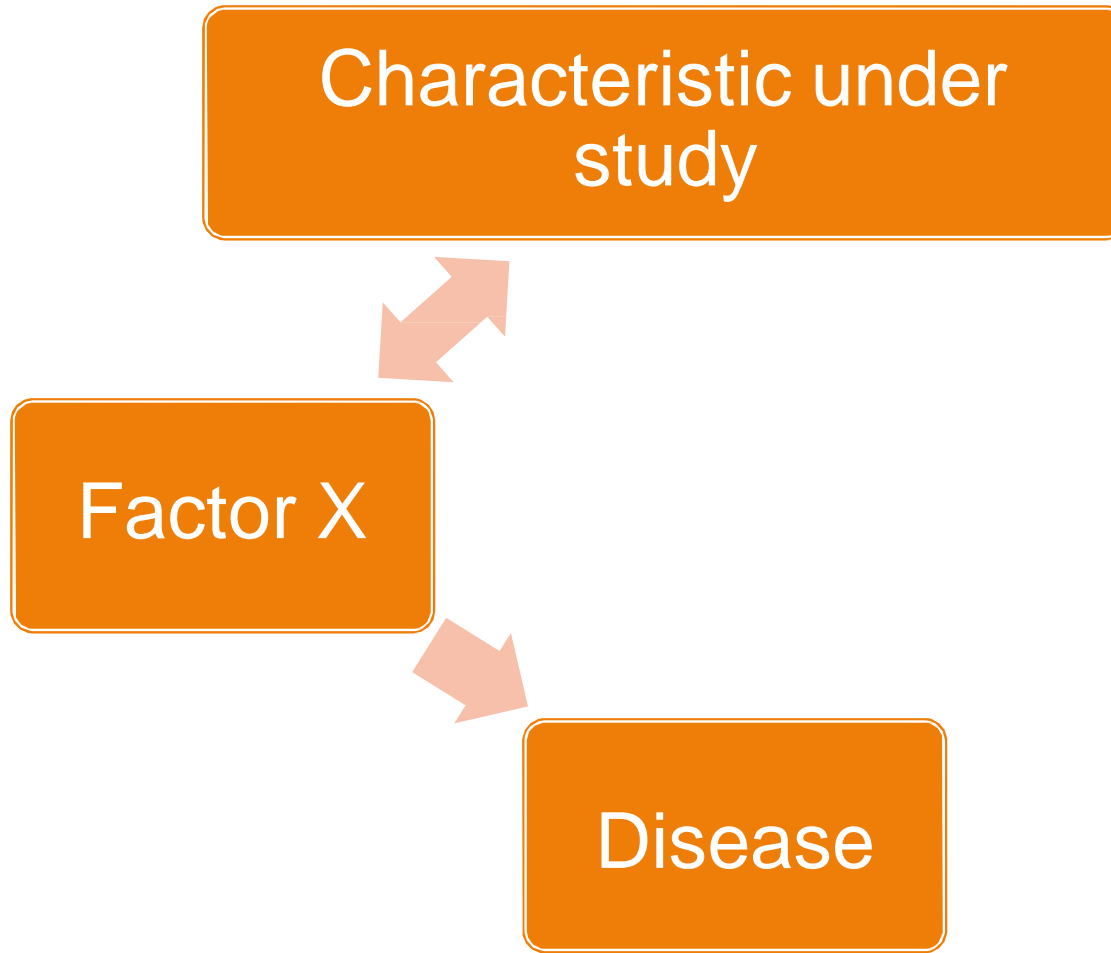
Types of Association

1. Spurious Association
2. Indirect Association
3. Direct (causal) Association
 1. One to one causal association
 2. Multi-factorial causation.

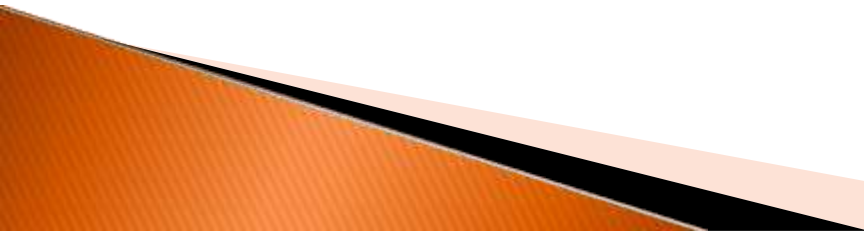
1. Spurious association

- ▶ False association
- ▶ Because of comparison of *likes* with *non likes* (*selection bias*)

2. Indirect association



Association or not?


- ▶ To address the question of association, we must use approaches that involve explicit comparisons.
 - ▶ Comparing the risk of disease in exposed population to the risk of disease in non exposed populations.
 - Ratio of the risks
 - Difference in the risks
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- ▶ A researcher in his observational study found that the average serum homocysteine among patients of IHD was 15 mcg/dl (Normal=10-12 mcg/dl)!


Implication

- ▶ Can we say that
 - Hyperhomocystenemia causes IHD?
- ▶ Hypothesize that
 - Hyperhomocystenemia **may** have a role in etiology of IHD.
- ▶ For final proof there has to be a 'comparison'.
- ▶ Comparison would generate another summary measure which shows the extent of 'Association' or 'Effect' or 'risk'

Cause

- ▶ Cause defined as “anything producing an effect or a result”. [Webster]
 - ▶ Cause in medical textbooks discussed under headings like- “etiology”, “Pathogenesis”, “Mechanisms”, “Risk factors”.
 - ▶ Important to physician because it guides their approach to three clinical tasks- **Prevention, Diagnosis & Treatment**. Eg.....
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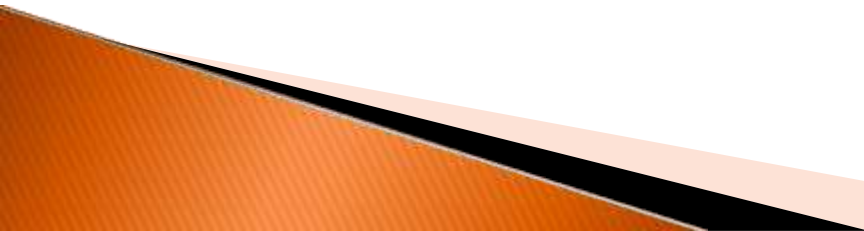
Examples

- ▶ **Prevention:** When clinicians periodically checks patients BP they are reacting to evidence that HT causes morbidity & mortality and that the treatment of hypertension prevents MI,CHF & stroke.
 - ▶ The **diagnostic** process, especially in infectious disease, frequently involves a search for the causative agent.
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Examples

- ▶ Belief in a causal relationship underlies every **therapeutic** intervention in clinical medicine.
- ▶ Why give azithromycin for pneumococcal pneumonia unless one believes that it will result in a cure.

Factors for disease causation

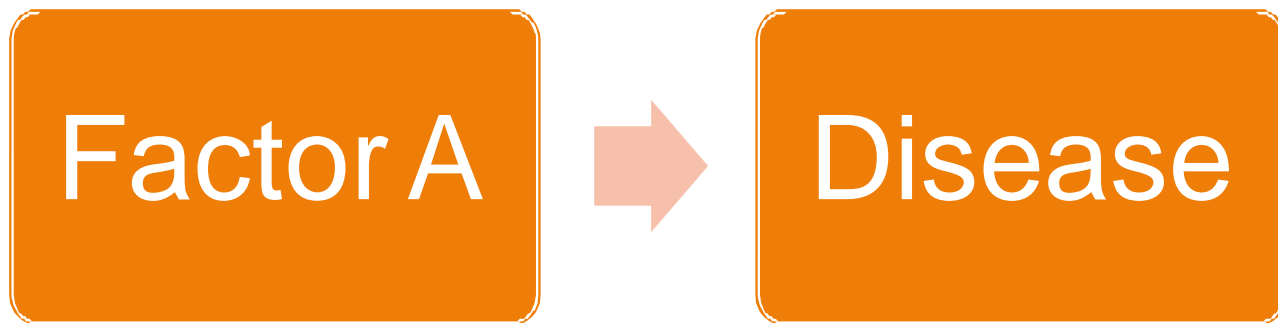
- ▶ **Sufficient f's:** one that inevitably produces disease
 - ▶ **Necessary f's:** without which disease does not occur, but by itself, it is not sufficient to cause disease.
- * **The factor which can be modified , interrupted or nullified is most important.**
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Types of Causal Relationships

- ▶ Four types possible
 - Necessary & sufficient
 - Necessary, but not sufficient
 - Sufficient, but not Necessary
 - Neither Sufficient nor Necessary

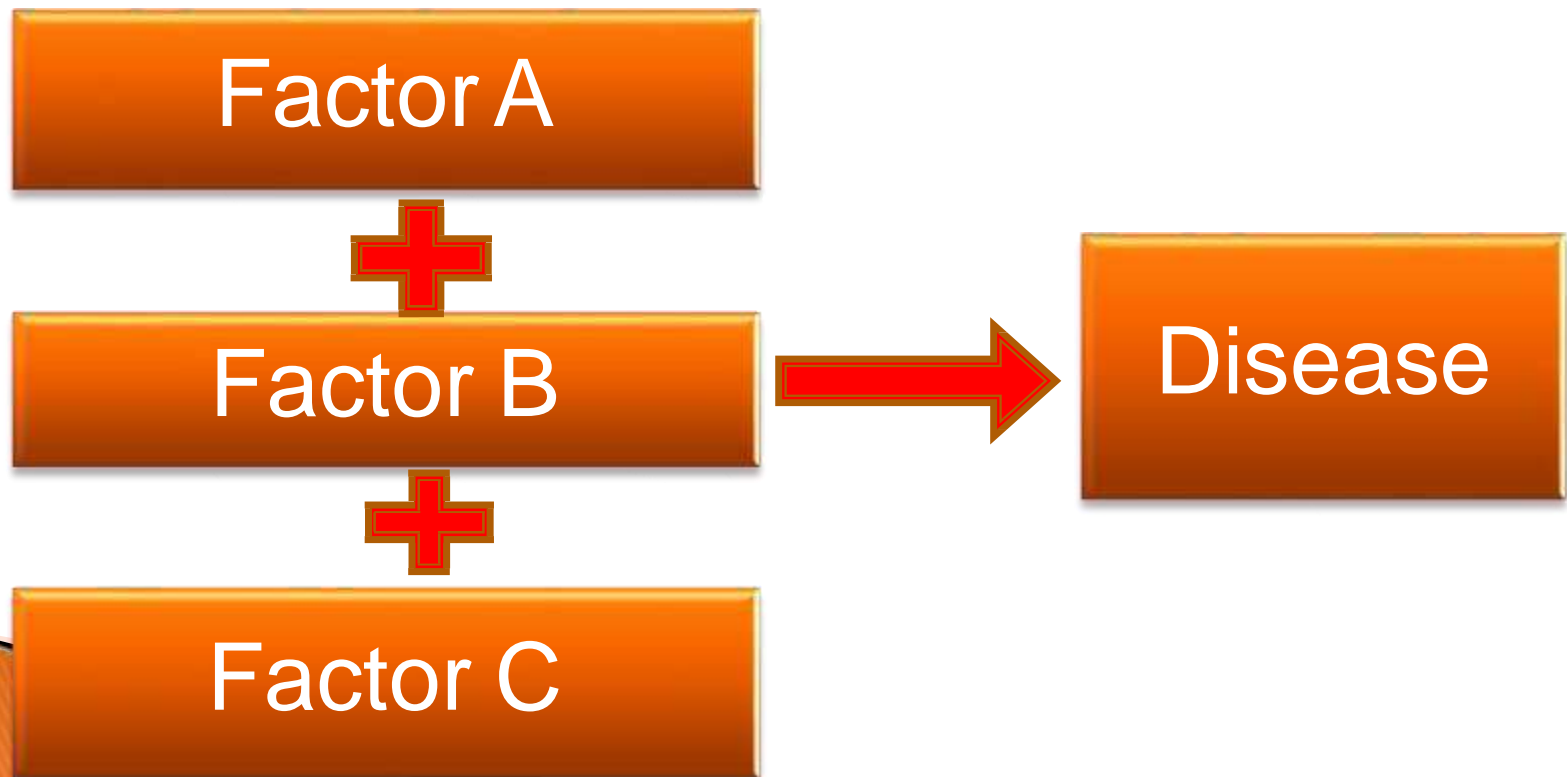
I. Necessary & Sufficient

- ▶ Without that factor, the disease never develops (**factor is necessary**)
- ▶ and in presence of that factor, the disease always develops (**factor is sufficient**).
- ▶ Rare situation.



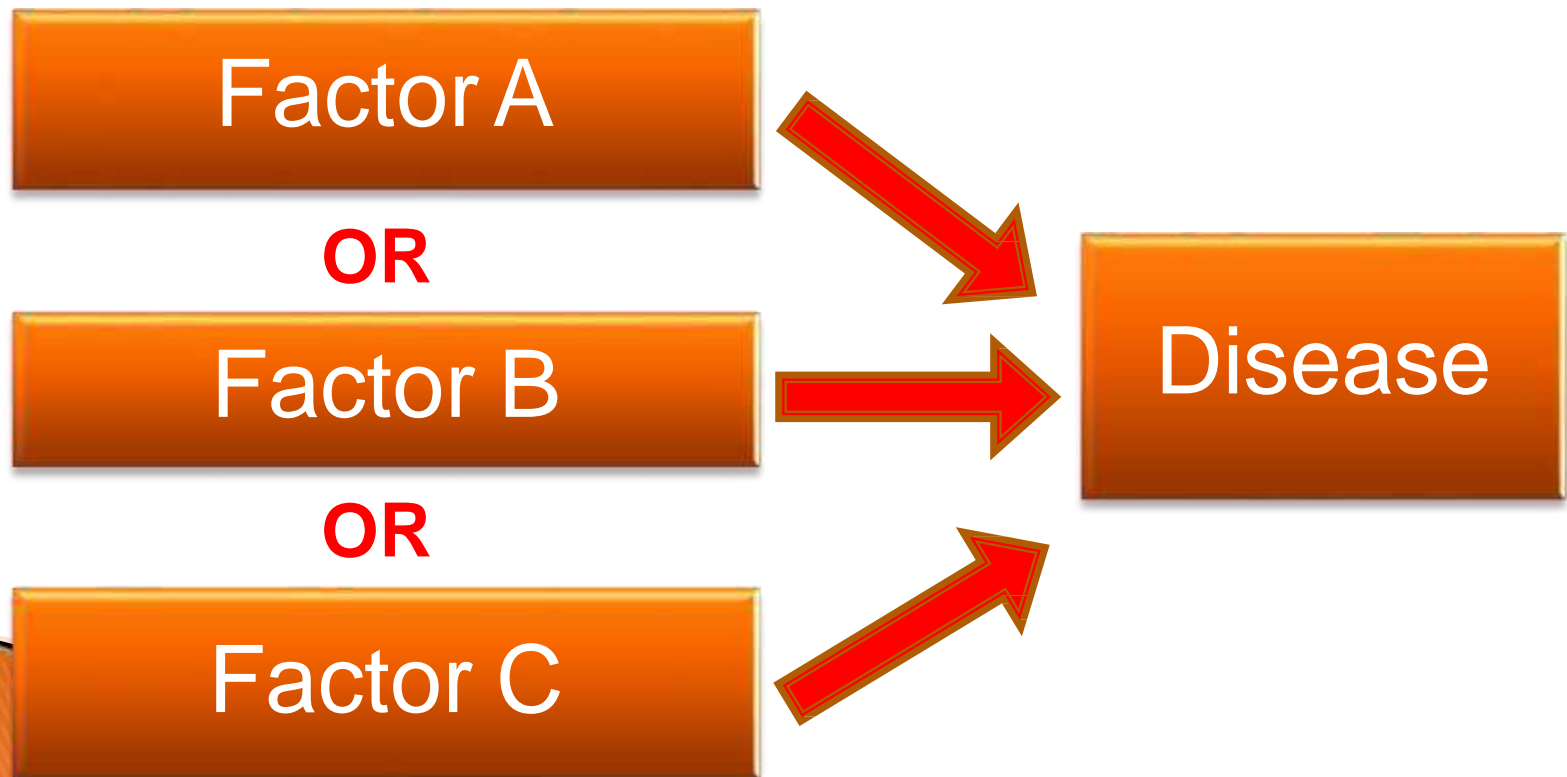
II. Necessary, but not Sufficient

- ▶ Multiple factors are required, often in specific temporal sequence.



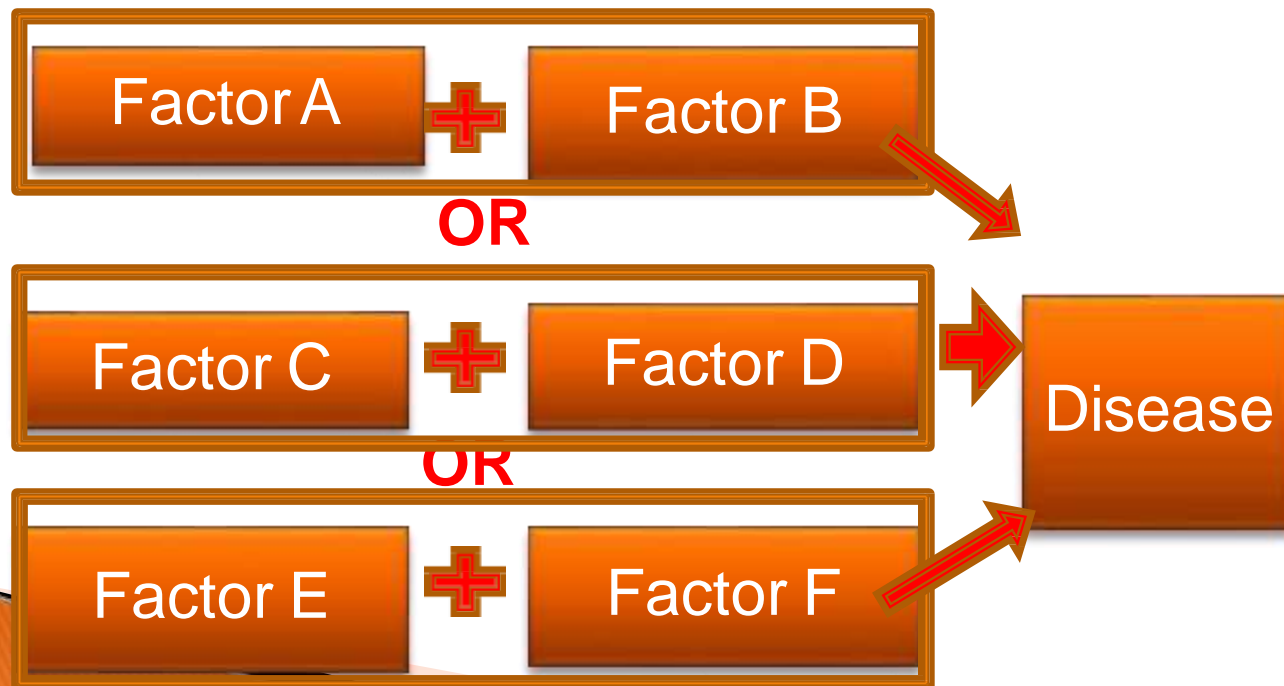
III. Sufficient, but not Necessary

- Factors independently can produce the disease.



IV. Neither sufficient nor Necessary

- More complex model.
- Probably most accurately represents causal relationships that operate in most chronic diseases



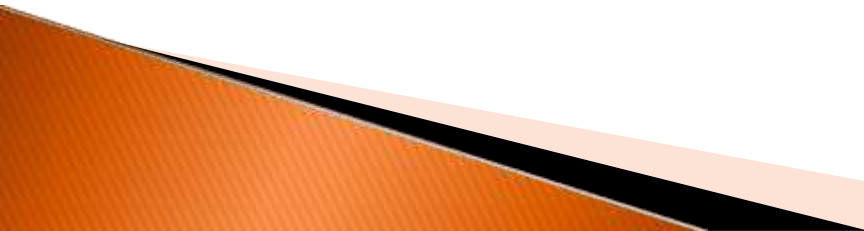
- ▶ A researcher in his observational study found the presence of *Helicobacter pylori* in patients of duodenal ulcer!

Implication

- ▶ Can we say that
 - H.pylori causes duodenal ulcers?
- ▶ Hypothesize that
 - H.pylori **may** have a role in etiology of duodenal ulcers.
- ▶ For final proof there has to be a 'comparison'.
- ▶ Comparison would generate another summary measure which shows the extent of 'Association' or 'Effect' or 'risk'

Process of establishing a “Cause & Effect” or “Exposure & Outcome” relationship

- ▶ Needs a research on the lines of ‘hypothesis testing’
- ▶ final establishment of an “exposure - outcome” relationship consists of a sequence of steps as follows :
- ▶ **Step 1:** ensure that the results of the study are accurate and not “spurious”.
 - Correct methods?
 - Validity, reliability preserved?
 - Bias?

- ▶ **Step 2a:** do statistical results indicate association?-p value/ 95% CI.
 - ▶ **Step 2b:** if not significant p value, may be b/c of less power (smaller sample size)- the investigator should suggest additional studies using large sample (or else, a 'meta - analysis' type of study), rather than straightaway dismissing the 'exposure - outcome' association as non - causal.
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- ▶ **Step 3:** if statistically significant –evaluate as to whether this relationship is due to ‘indirect relationship’ with a third variable (confounder)

- ▶ *In what circumstances can we pass from [an] observed association to a verdict of causation? Upon what basis should we proceed to do so?*



Sir Austin Bradford Hill, 1965

- ▶ **Step 4:** if confounder excluded- now test this postulated “causal” relationship on the following criteria of “causal association”

Guidelines for judging whether an association is causal

▶ Most Important criteria

1. **Temporality:** cause precedes effect
2. **Strength of association:** large relative risk
3. **Consistency:** repeatedly observed by different persons, in different places, circumstances, and times

Guidelines for judging whether an association is causal

▶ Additional supportive criteria

4. **Biological gradient (dose response):** larger exposures to cause associated with higher rates of disease. And reduction in exposure is followed by lower rates of disease (reversibility).
5. **Biological plausibility:** makes sense, according to biologic knowledge of the time.
6. **Experimental evidence:**
7. **Other criteria: Analogy**(cause & effect relationship already established for a similar exposure or disease), **specificity** (one cause lead to one effect), **coherence**.

1. Temporal relationship

- ▶ Order of exposure and disease.
- ▶ Interval between exposure and disease.
 - **E.g.** Asbestos has been clearly linked to increased risk of lung cancer but the latent period between exposure and appearance of cancer is 15-20 yrs. Therefore, if for e.g. lung cancer develops after only 3 yrs since the asbestos exposure, it is safe to conclude that the lung cancer was not a result of this exposure.

2. Strength of association

- ▶ Measured by the Relative risk (or Odds ratio)
- ▶ Stronger the association, the more likely it is that the relation is causal.

3. Dose response relationship

- ▶ Strong evidence for a causal relationship.
- ▶ However, the absence of a dose response relationship does not necessarily rule out a causal relationship.
 - E.g. those cases in which a threshold exist.
 - The association b/w DES consumption by mothers and vaginal CA in daughters many years later does not exhibit this gradient phenomenon.

4. Replication of the findings

- ▶ If the relationship is causal, we would expect to find it consistently in different studies and in different populations, even within subgroups of populations.

5. Biological plausibility


- ▶ Refers to coherence with the current body of biologic knowledge.
 - E.g. In the mid 19th century when a clinician recommended hand washing by medical students & teachers before attending obstetric units, his recommendations were dismissed by medical fraternity as “doesn’t stand to reasoning”

Opposing View: Discovery of Preventive Measure May Predate Identification of Definitive Cause

| Disease | Discoverer of preventive measure ^a | Year of discovery of preventive measure | Year of discovery of agent | Causative or preventive agent ^b | Discoverer of agent ^a |
|-----------------------------|---|---|----------------------------|--|----------------------------------|
| Scurvy | J. Lind | 1753 | 1928 | (Ascorbic acid) | A. Szent-Gyorgi |
| Pellagra | G. Casal | 1755 | 1924 | (Niacin) | Goldberger et al. |
| Scrotal Cancer | P. Pott | 1755 | 1933 | Benzo[<i>a</i>]pyrene | J. W. Cook et al. |
| Smallpox | E. Jenner | 1798 | 1958 | Orthopoxvirus | F. Fenner |
| Puerperal fever | I. Semmelweis | 1847 | 1879 | Streptococcus | L. Pasteur |
| Cholera | J. Snow | 1849 | 1893 | <i>Vibrio cholerae</i> | R. Koch |
| Bladder cancer ^c | L. Rehn | 1895 | 1938 | 2-Napththlamine | Hueper et al. |
| Yellow fever | W. Reed et al. | 1901 | 1928 | Flavivirus | A. Stokes et al. |
| Oral cancer ^d | R. Abbe | 1915 | 1974 | <i>N</i> -nitrosornicotine | Hoffmann et al. |

What if we waited until the mechanism was known before employing citrus?

6. Consideration of Alternate Explanations

- ▶ Whether the relationship is causal or is the result of confounding, the extent to which the investigators have taken other possible explanations into account & the extent to which they have ruled out such explanations are important considerations.
 - ▶ Helpful supportive evidence for a causal association
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7. Cessation of exposure

- ▶ If a factor is a cause of a disease , we would expect the risk of the disease to decline when exposure to the factor is reduced or eliminated.

8. Consistency with other knowledge



9. Specificity of the association

- ▶ Weakest of all the guidelines.
- ▶ When a certain exposure is associated with only one disease.

Assessment of evidence suggesting H.pylori as a causative agent of duodenal ulcers

1. **Temporality:**

- About 11% of chronic gastritis patients will go on to have duodenal ulcers over a 10year period.

2. **Strength of relationship:**

- H.pylori is found in at-least 90% of patients with duodenal ulcers.
An Australian tribe population lacking duodenal ulcers, it has never been found.

3. **Dose response relationship:**

- density of H.pylori per square mm of gastric mucosa is higher in patients with duodenal ulcer than without it.

Assessment of evidence suggesting H.pylori as a causative agent of duodenal ulcers

4. **Replication of findings:**

- many observations regarding H pylori have been replicated repeatedly.

5. **Biologic plausibility:**

- it was difficult to envision a bacterium infecting stomach antrum with such high acidity, but it is now recognized that H pylori has binding sites on antral cells.

6. **Consideration of alternate explanations:**

- data suggest that smoking can increase the risk of duodenal ulcer in H pylori infected patients but is not a risk factor in patients in whom H pylori has been eradicated.

Assessment of evidence suggesting H.pylori as a causative agent of duodenal ulcers

7. **Cessation of exposure:**

- long term ulcer recurrence rates were zero after H pylori was eradicated using triple antimicrobial therapy, compared with a 60-80% relapse rate found in those treated with histamine receptor antagonists.

8. **Specificity of association:**

- prevalence of H pylori in patients with duodenal ulcers in 90-100% vs found in some patients with gastric ulcer/asymptomatic individuals.

Assessment of evidence suggesting H.pylori as a causative agent of duodenal ulcers

9. Consistency with other knowledge:

- H pylori infection prevalence is same in men & women in recent years which was believed to be higher in men.
- High prevalence of ulcer disease in latter part of 19th century, consistent with high prevalence of H pylori due to poor living conditions at the same period.

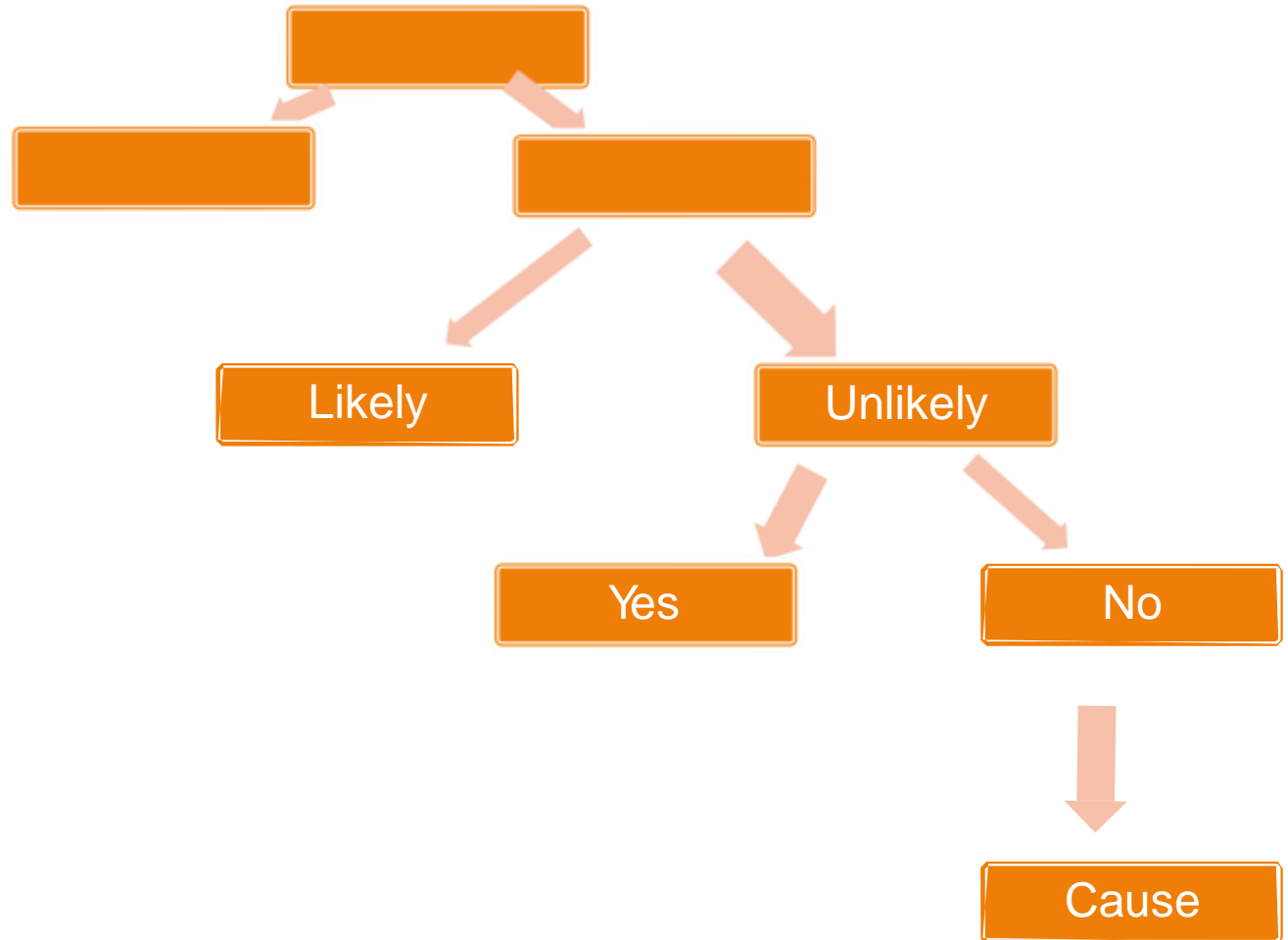
From Association to Causation

**Bias in
selection or
measurement**

Chance

Confounding

Cause



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Evidence

▶ **Weighing the Evidence**


- Its not the total no of guidelines present that is relevant to causal inference but rather an assessment of total pattern of evidence observed that may be consistent with one or more of the guidelines.

▶ **Grading the Quality of Evidence**

Susser's criteria (I)

- ▶ Mervyn Susser (1988) used similar criteria to judge causal relationships.
- ▶ In agreement with previous authors, he mentioned that two criteria have to be present for any association that has a claim to be causal: i.e. **time order** (X precedes Y); and **direction** (X leads to Y).

Susser's Criteria (II)

- ▶ **Rejection** of a hypothesis can be accomplished with confidence by only **three criteria**: time order, consistency, factual incompatibility or incoherence.
 - ▶ **Acceptance or affirmation** can be achieved by only four, namely: strength, consistency, predictive performance, and statistical coherence in the form of regular exposure/effect relation.
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Comparison of Causal Criteria

CAUSAL CRITERIA COMPARED

| SURGEON GENERAL | SUSSER | BRADFORD-HILL |
|-----------------|---------------------------|----------------|
| | ASSOCIATION | DOSE RESPONSE* |
| | DIRECTION | EXPERIMENT |
| TIME ORDER | TIME ORDER | TIME ORDER** |
| STRENGTH | STRENGTH | STRENGTH |
| CONSISTENCY | CONSISTENCY | CONSISTENCY |
| SPECIFICITY | SPECIFICITY | SPECIFICITY |
| COHERENCE | COHERENCE | COHERENCE*** |
| | PREDICTIVE PERFORMANCE | |

*Included under strength in other criteria. ** Temporality in Bradford-Hill. *** Biological plausibility in Bradford-Hill