NOVEL BIOMARKERS AS RISK FACTORS FOR CARDIOVASCULAR DISEASE

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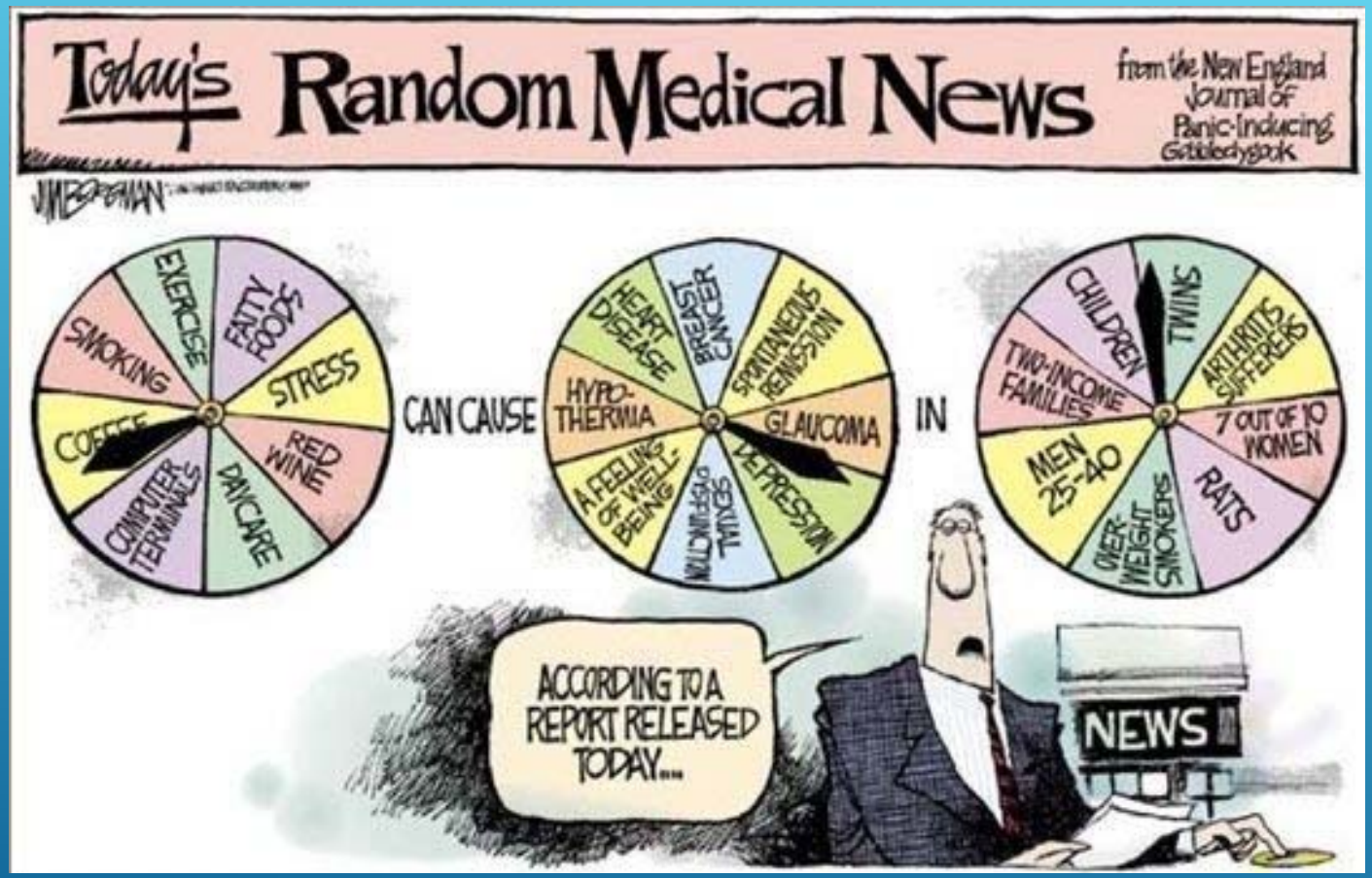
CAUSE VERSUS MECHANISM

- Causation is a concept central to epidemiology
- Etiology of CVD
  - Onset of atherosclerosis
  - Promote plaque development
  - Precipitate a clinical event
- Biomarkers may be causal, a measure of the underlying pathology, or a correlate of a causal factor



Borgman J. Today's random medical news from the New England Journal of Panic-Inducing Gobbledygook (cartoon). Cincinnati Enquirer. 1997

- Strength of Association
- Consistency of the Association
- Specificity
- Temporality
- Biologic Gradient (i.e., dose-response)

HILL'S POSTULATES OF CAUSATION FOR CHRONIC DISEASES

WHAT DEFINES A "MAJOR" RISK FACTOR?

- Extensive, multidisciplinary study demonstrating significant role in etiology of CVD
- High prevalence
- Strong impact on risk
- Guidelines for optimal levels
- Potential for prevention or treatment (for modifiable factors)

MAJOR RISK FACTORS FOR CVD

- Modifiable
  - Diabetes
  - Obesity and overweight
  - Smoking
  - High cholesterol
  - High blood pressure
  - Physical inactivity
  - Poor diet
- Unmodifiable
  - Age
  - Family history

IMPACT OF MAJOR RISK FACTORS

- Improvements in modifiable risk factors can significantly decrease cardiovascular morbidity and mortality*.
  - A recent meta-analysis found that achieving the greatest AHA ideal health metrics was associated with significantly lower risk of stroke, CVD, and CVD mortality.
  - Trends in improvement of these cardiovascular health metrics are projected to reduce CHD mortality by 30% by 2020.
- Lifetime risk of CVD events varies depending on age, gender, and presence of major modifiable risk factors†.
  - With an optimal risk factor profile, risk varies between 0.9% and 29.5%
  - With ≥2 major risk factors present, risk varies between 9.1% and 49.5%

*Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017;135:e146-e603.
†Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. The New England journal of medicine 2012;366:321-9.

AND YET…

- Traditional risk factors account for between 50% and 82% of the risk of CVD
- Significant gaps remain in understanding other contributors to CVD

NOVEL BIOMARKERS

- Inflammation
- Adiposity – distribution and deposition in fat depots
  - Epicardial/pericardial fat
  - Liver fat
- Genetics
- Infections
  - *Chlamydophila pneumonia*
  - Periodontal disease

DEFINITION OF PERIODONTAL DISEASE

- A chronic inflammatory lesion of the supporting structures surrounding the teeth
- Shift in composition of oral microbial ecology from predominately Gram-positive organisms to anaerobic Gram-negative organisms
- Disease pathogenesis is mediated by the immune response to chronic infection
- Characterized by local and systemic inflammation

- Dissemination of bacterial components (LPS)
- Local and systemic production of cytokines (IL-1β, TNF-α, IL-6)
- Spill-over of local cytokines into circulation
- Increases in peripheral leukocytes (primarily neutrophils)

SYSTEMIC INFLAMMATION DUE TO PERIODONTAL DISEASE

PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE

- "Hyperinflammatory phenotype"
  - Secretion of increased levels of proinflammatory cytokines
  - Dysfunction in mechanisms of immune resolution
- Atherosclerosis is an inflammatory condition
- Observations of increased risk of cardiovascular disease due to infection and inflammation
- Risks of bacteremia

EVIDENCE OF ASSOCIATION

- Recent meta-analysis from 22 observational studies showed statistically significant association with MI risk [OR = 2.02 (1.59 – 2.57)]*
- Growing body of literature on the oral-systemic connection
  - Rheumatoid arthritis
  - Preterm birth
  - Osteoporosis
  - Diabetes

*Xu S, Song M, Xiong Y, Liu X, He Y, Qin Z. The association between periodontal disease and the risk of myocardial infarction: a pooled analysis of observational studies. BMC Cardiovasc Disord 2017;17:50

LIMITATIONS OF PREVIOUS STUDIES

- Lack of association in some studies; moderate association in others
- Lack of control for confounding, particularly smoking
- Potential for residual confounding
- Lack of measure of the infection
- Inconsistent definitions for both cardiovascular disease and periodontal disease

POTENTIAL MECHANISMS

- Indirect: systemic inflammation
- Direct: bacteremia and colonization of atheroma by periodontal pathogens
- Host factors
  - Genetic susceptibility
  - "Hyperinflammatory"
  - Co-morbidities

- Which mechanism, if any or all, is not understood
- Exact molecular processes are not known
- Where in the atherosclerotic process is the effect exerted? Initiation, enhancement of early processes, accelerated progression, or precipitation of events?

QUESTIONS

UNDERSTANDING THE INFECTION

- Clinical measures
  - Historical insight
  - Capture effect of infection and immune response
  - Lack understanding of bacterial processes
- Measuring antibodies
- Culture methods

METAGENOMIC SEQUENCING

- Nucleotide sequencing techniques that allow identification of composition of the microbiome in various sites
  - Oral (saliva, subgingival, supragingival)
  - Gut
  - Skin
- Relative abundance and diversity
- Dysbiosis in the microbiota is associated with
  - Periodontal disease
  - Inflammatory bowel disease
  - Cancer

ONGOING RESEARCH

- Composition of microbiome in various sites
- Function of microbiome
  - Transcriptomics
  - Proteomics
  - Metabolomics
- Mycobiome
- Virome

PERSONALIZED MEDICINE

- Bacterial signatures
  - Higher risk of disease
  - Treatment efficacy
- Targeted treatment
  - Microbiome transplant
  - Treatment to alter microbiome