Connecting Cause to Consequence

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The Context of Scientific Evidence

**Fact** = a truth known by actual experience

**Oversimplified** = Simplified to the point of causing error, misrepresentation, or misconception; = facts out of context

**Paradox** = an opinion contrary to received opinion; = an apparent self-contradiction that is explained by added truthful information

**Fiction** = an imaginative narration; = allegation that a fact exists which is known not to exist; = a story invented to deceive

**Hypothesis** = a fiction not yet proved as fact (i.e. to be disproved)
Often-neglected facts cause paradoxes:

An association with disease is not proof of cause.

Removing disease signs & symptoms, may not remove the cause.
HOW FOOD HARMS
(1.7 minutes)
Excess food energy causes transient events with every meal.

FOOD
- amino acids
- nucleosides
- fatty acids
- sugars
- essential FA

acetyl-CoA
- malonyl-CoA
- HMG-CoA
- mevalonate
- isoprenoids
- prenylated proteins
- oxidant stress & inflammation & proliferation & impaired nitric oxide
- vessel wall plaques
- platelet activation
- thrombosis
- ischemia
- arrhythmia

\( \text{CO}_2 + \text{electrons} \rightarrow \text{acetyl-CoA} \rightarrow \text{malonyl-CoA} \rightarrow \text{HMG-CoA} \rightarrow \text{mevalonate} \rightarrow \text{isoprenoids} \rightarrow \text{prenylated proteins} \rightarrow \text{oxidant stress & inflammation & proliferation & impaired nitric oxide} \rightarrow \text{vessel wall plaques} \rightarrow \text{platelet activation} \rightarrow \text{thrombosis} \rightarrow \text{ischemia} \rightarrow \text{arrhythmia} \rightarrow \text{Morbidity & Mortality} \)

\( \text{Fatty acyl-CoA} \rightarrow \text{VLDL} \rightarrow \text{FFA} + \text{LDL cholesterol} \)

\( \text{CO}_2 + \text{electrons} + \text{H}_2\text{O} \rightarrow \text{ATP} + \text{ADP} \rightarrow \text{work exercise synthesize} \)

Biomarkers
- Triglyceridemia
- Obesity
- Insulin resistance
- Elevated glucose

Transient Postprandial insults

Excess food energy causes transient events with every meal.
Cholesterol and all-cause mortality in Japan (meta-analysis)

Five reports were included in this metaanalysis. Reports excluded were published before 1995, based on a cohort of less than 5000 subjects, or contained no information about the number of deaths in each cholesterol group. The width of each column is proportional to the number of subjects in that group. The total number of subjects: 173,539. *: p=0.02, **: p<0.0001.

Food energy imbalances which raise blood cholesterol may be fatal only to the degree that omega-6 (n-6) EXCEEDS omega-3 (n-3) in tissue HUFA.
HOW OMEGA-6 IN FOOD HARMS (1.0 minute)
FOOD
- amino acids
- nucleosides
- fatty acids
- sugars
- essential FA

Biomarker
- % n-6 in HUFA of tissue phospholipids

n-3 & n-6 HUFA release

XS n-6 hormones

aspirin

platelet activation

vessel wall plaques

ischemia

thrombosis

arrhythmia

oxidant stress & inflammation & proliferation & impaired nitric oxide

Morbidity & Mortality

Connecting primary cause to consequences

A valid surrogate endpoint for nutrition-based primary prevention of CHD morbidity & mortality
High %n-6 in HUFA is a valid surrogate endpoint to prevent.

Choose valid surrogate endpoints for effective prevention.

http://efaeducation.nih.gov/sig/chainofevents.ppt
A 1978 European questionnaire had two items:
1. “Do you think there is a connection between plasma cholesterol level and the development of coronary heart disease?” (189, yes; 2, no)
2. “Do you think that our knowledge about diet and coronary heart disease is sufficient to recommend a moderate change in the diet for the population in an affluent society?” (176, yes; 16, no).

The 1984 NIH Consensus Development Panel regarded CHD as a diet-induced disease caused by imbalanced food energy. It urged that the first step in treatment should be caloric restriction and weight loss, and that “even when use of drugs seems appropriate, it is important to stress that maximal diet therapy should be continued”.

Nevertheless, the 1984 Panel voted:
1. “Is the relationship between blood cholesterol levels and coronary heart disease causal?” (14, yes; 0, no)
2. “Should an attempt be made to reduce blood cholesterol levels of the general population?” (14, yes; 0, no)

The Panel report “figured very large” in the FDA decision to justify approval of cholesterol-lowering therapy without requiring the manufacturers to submit at the time of application clinical trial data demonstrating efficacy.
Connecting primary cause to consequences

Clinical trials treat indirect biomarkers

FOOD
- amino acids
- nucleosides
- fatty acids
- sugars
- essential FA

Biomarker
- % n-6 in HUFA of tissue phospholipids
- n-3 & n-6 HUFA release
- XS n-6 hormones
- aspirin

acetyl-CoA
- malonyl-CoA
- HMG-CoA
- statin
- mevalonate
- isoprenoids
- prenylated proteins
- oxidant stress & inflammation & proliferation & impaired NO

VLDL
- cholesterol
- squalene

FFA
- + LDL cholesterol

Biomarkers
- Triglyceridemia
- Obesity
- Insulin resistance
- Elevated glucose

Excess food energy causes transient insults with every meal

Morbidity & Mortality
- platelet activation
- vessel wall plaques
- thrombosis
- ischemia
- arrhythmia

ENHANCE
- ACCORD
- ADVANCE
- VA-Diabetes

Also CRP

Jupiter
2008 mass media comments on LDL-cholesterol limits in CHD

http://www.businessweek.com/print/magazine/content/08_04/b4068052092994.htm
http://www.businessweek.com/print/bwdaily/dnflash/content/mar2008/db20080331_704360.htm
http://www.businessweek.com/print/bwdaily/dnflash/content/apr2008/db20080414_050826.htm


Press release: Oct., 2008 - Pfizer will end early-stage development of cardiovascular treatments in favor of more profitable areas, such as anticancer, anti-inflammatory, psychoses (schizophrenia), pain, Alzheimer's disease, and diabetes candidates.

Test for blood omega-3 levels can be very important in preventing CHD.

CRP test results may be more useful than cholesterol levels to promote statin use.
Efficacy of Clinical Interventions

Meta-analysis of 97 randomized controlled trials with 137,140 people in intervention & 138,976 in control groups

Risk Ratios for Overall Mortality

1.00 for fibrates (no better than control)
0.97 for “diet advice”
0.96 for niacin
0.87 for statins
0.84 for resins
0.77 for n-3 fatty acids (less risk than control)

Americans have excessive omega-6 in HUFA & an omega-3 deficit

CHD Mortality and Tissue HUFA

\[ y = 3.0323x - 74.8 \]
\[ R^2 = 0.9866 \]

Primary Prevention happens here

A high % omega-6 means Omega-3 deficit

Americans have excessive omega-6 in HUFA & an omega-3 deficit

Lands, Lipids 2003 (Apr.); 38: 317–321
http://efaeducation.nih.gov/sig/personal.html
Adjust Ambient Intakes to Decrease Risk of CHD

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<th>Lower est. UL n-6LA</th>
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data = Hibbeln et al, AJCN 2006

data = http://efaeducation.nih.gov/sig/dietbalance.html
Effective Primary Prevention Needs You

**TO UNDERSTAND**–

Food energy causes **transient** tissue insults
Omega-6 hormones **amplify** insults into inflamed injuries
Omega-3 HUFA **diminish** inflammatory insults

**TO TEACH** -

**EAT MORE OMEGA-3**

**EAT LESS OMEGA-6**

**EAT FEWER CALORIES PER MEAL**
Distant learning website for essential fatty acids and eicosanoids
http://efaeducation.nih.gov/

Distant learning website for calculating tissue HUFA balance
http://efaeducation.nih.gov/sig/dietbalance.html

Choose daily foods to balance tissue HUFA using interactive software, KIM-2
http://efaeducation.nih.gov/sig/kim.html