

Ask a Question, Extract an Answer

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In a classic tale set in the Warsaw ghetto 65 years ago, a Nazi stormtrooper encounters frustration with one of the ghetto's inhabitants. Asks the stormtrooper: "Why is it that you people always question everything under the sun?" To which the resident replies: "Why not?" For those who might look upon researchers with a jaundiced eye and ask: Do they ever really solve a problem, or do they just find ways to raise more questions so as to remain gainfully employed? Take heart. The system is rigged. Nature never has shared her answers easily, nor have scientific answers ever remained etched in stone. Scientific history, as we all know, is replete with upheavals and revolutions of thought. Let us consider just a couple of the most recent clinical examples.

For decades, after having managed to fractionate cholesterol into high- (HDL) and low-density (LDL) fractions, we have been able to come to the conclusion that [HDL is the "good" cholesterol](#) since it transports cholesterol to the liver for excretion and recycling, removing it from the arteries.¹ Not quite so simple, it turns out. We now find out that HDL cholesterol consists of no less than 13 subclasses of proteins that can be separated by two-dimensional high-resolution chromatography. Patients with coronary artery disease have less of one of these subclasses (called 1) but elevated levels of another (3), which is associated with increased risk.^{2,3} How does one digest this new information? Not by throwing the baby out with the bathwater (or HDL out with LDL, for that matter), but gaining a sharper probe into what elements of cholesterol are most beneficial and which are not.

The going gets really tough when we look into the saga of folic acid, which has almost achieved the level of aspirin as a universally effective and safe occupant of one's medicine chest. Here are the proposed benefits: important in [preventing neural tube defects](#) in infants,⁴ important in [preventing cervical dysplasia](#)⁵ and an important nutrient for preventing [atherosclerosis associated with elevated homocysteine](#).⁶ Now here's the negative evidence:

- A randomized clinical trial at nine clinical centers with 1,021 subjects: [did not reduce risk of colorectal adenoma](#).⁷
- The Heart Outcomes Prevention Evaluation (HOPE-2) RCT: B vitamins and folate [did not show a benefit in cardiovascular disease \(CVD\) reduction](#); however, there was a 25 percent reduction in strokes.⁸
- Vitamins Intervention for Stroke Prevention: [no CVD benefit](#).⁹
- [Norwegian Vitamin Trial \(NORVIT\)](#): no CVD benefit.¹⁰
- Cambridge Heart Antioxidant Study (CHAOS-2): no CVD benefit.¹⁰
- [Western Norway B Vitamin Intervention Trial \(WENBIT\)](#): no CVD benefit.¹⁰
- Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS): [no CVD or stroke benefit](#).¹¹

This is not simply raining on one's parade. It's more like an avalanche of negativity. How does one begin to explain away or rationalize this torrent of contrary research findings? Again, the answer is

to be able to raise more pointed and insightful questions regarding the circumstances in which the observations were made. Such extenuating circumstances would include these facts:

- Folic acid was mandated to be added to white flour, cereal grains and related products in the U.S., resulting in [lowered endogenous homocysteine levels in domestic subjects](#).¹² The result would be to obscure the effects of folate added experimentally.
- The studies may have been underpowered.¹²
- Homocysteine may have been measured in only a small proportion of the study participants.¹²
- The study participants may have relatively low CVD rates compared to the general population.¹²
- Folate apparently has an effect upon the methylation rates of promoter regions of the chromosome, the pro-atherosclerotic effects of which may have offset the benefits associated with the lowering of homocysteine.^{13,14}

Other than preventing neural tube defects, has folate been knocked out of the ring with these new findings? There are cognitive-acuity findings that still support the wisdom of preventing folate deficiencies in humans, but even here there are contrary data.^{15,16} A recent British study has found that [elevated plasma homocysteine, but not reduced folate levels](#) predict mortality in older people.¹⁷ So, the answer to this conundrum appears to be that folate may have certain benefits and may or may not be instrumental in lowering toxic homocysteine levels. However, its effects regarding CVD and stroke may be limited or nonexistent.

The overall message is that natural phenomena are commonly more complex than first assumed and require a great deal of sophistication in order to be able to account for all its effects. The only way to achieve these more advanced levels of understanding is to be able to soldier on with more finely honed and enlightened research questions that can only be derived from conundrums such as the ones just discussed. In other words, nature is a lot smarter than we are. It will take both humility and perseverance to be able to gain the understanding and control we seek in scientific research.

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