

## VARIANCE AND DISSENT

### Response

## Reply to the Dissent by W.S. Weintraub

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In my review [1], I outlined the various ways in which researchers treat scientific results that run contrary to their hypothesis. Interestingly, all of them have been used by Professor Weintraub in his comments. To categorize each method, I have used Roman numerals as follows:

- I. Introducing ad hoc modifications to the theory
- II. Citing irrelevant facts or studies
- III. Citing supportive or allegedly supportive studies only
- IV. Inflating insignificant findings
- V. Ignoring contrary studies
- VI. Citing contradictory studies as if they were supportive

### **The alleged causal link between dietary fat and cardiovascular disease**

Weintraub admits that the epidemiological data for diet are “somewhat imperfect”; however, the new evidence he presents does not improve the situation [2]. For instance, his argument, the parallel decline of heart mortality and saturated fatty acid (SFA) consumption, which originated in the US in the 1960s (III), is counterbalanced by an increase in heart mortality, an increase in margarine consumption, and a decrease of SFA consumption during the preceding 40–50 years (V) [3]. Inverse trends of heart mortality and SFA consumption have occurred in many other countries, which brings me to Golomb’s response to my previous review (used by Weintraub as an argument): that parallel changes have occurred in more countries ( $n = 30$ ) than have inverse changes ( $n = 23$ ). This may simply be a result of chance, however; furthermore, the fact that 23 studies directly contradict the diet–heart hypothesis should be a sufficient body of evidence to disprove the hypothesis completely.

Weintraub also ignores the unsupportive meta-analyses of the dietary trials (V) [4–6]. Instead he mentions two allegedly successful trials (III) [7,8]; however, these trials were multifactorial and thus cannot tell us anything about the effect of dietary fat. Weintraub also seeks support in three dietary trials that used an increase of fish or omega-3 polyunsaturated fatty acids (PUFAs) as the main intervention, as well as a number of epidemiologic studies that suggest a beneficial effect of these fatty acids (II, III). It is beyond doubt that these effects have nothing to do with cholesterol

[9]. What I question, however, is the idea that an increase in PUFA is beneficial. The main bulk of PUFA is omega-6 fatty acids, present in large amounts in most vegetable oils, and their effects on many biological functions are the exact opposite to the effects of omega-3 fatty acids. It is most unfortunate, therefore, that increased PUFA consumption, which is seen in many countries because of dietary recommendations, concerns mainly omega-6 fatty acids. (The reason why the dietary advice given previously has changed from “low SFA-high PUFA” to “low-fat” seems to be the negative effects of an excess of omega-6 fatty acids, but why has the public not been informed properly?)

I admit that there are great difficulties associated with the acquisition of reliable dietary data. My main concern, however, is that proponents of the diet–heart hypothesis have continued to support it with these imperfect, mostly contradictory studies. Weintraub does the same by referring to “The Cholesterol Facts” [10]. I have previously demonstrated that the authors of that review have ignored or misquoted all contradictory studies (II–V) [11].

### **The alleged causal link between high cholesterol and atherosclerosis**

The lack of an association between cholesterol levels and atherosclerosis is explained away by introducing a new hypothesis: it is oxidized cholesterol that matters (I); however, this is not the hypothesis that I question in my review. And if the hypothesis is right, it seems unusually bad advice to increase dietary PUFA. If any group of fatty acids may contribute to an oxidation of cholesterol, it is the polyunsaturated ones, not, as Weintraub claims, the saturated ones.

Weintraub returns to the original hypothesis by referring to the animal studies. May I remind him that what has been produced in almost all of these experiments is not atherosclerosis but fatty streaks, and also that no one has ever succeeded in producing a heart attack in an animal solely by raising its cholesterol.

Weintraub refers to a study of arterial changes in young people [12]; however, the changes in that study were neither correlated with low-density lipoprotein (LDL) or total cholesterol (V).

As evidence of the causal role of cholesterol on atherosclerosis, Weintraub mentions the predictive value of high cholesterol on coronary events (II) and the association between obesity and atherosclerosis (II). The relevance of these findings is not obvious to me.

### The alleged causal link between high cholesterol and coronary heart disease

First, epidemiologic studies of the association between high cholesterol and future coronary heart disease (II) do not prove causality; high cholesterol may only be a marker, just as fever is a marker of infectious diseases.

Weintraub admits that the results from the statin trials alone do not prove that the effect is due to cholesterol lowering, but adds that other ways of cholesterol lowering are also effective. He ignores that meta-analyses of the nonstatin trials found no effect, either on coronary or total mortality [13]. Instead, he mentions the nonblinded POSCH study that was biased by a more than 5 kg weight loss in the treatment group (IV), and also two of the three gemfibrozil trials, the Helsinki Heart study, and the VA-HIT trial, one of which resulted in a higher mortality in the treatment group. Why doesn't Weintraub mention the third gemfibrozil trial, the secondary preventive arm of the Helsinki trial [14], in which, if a group named "unwitnessed deaths" is included, there were three times as many fatal heart attacks in the treatment group (III, V, VI)?

Weintraub's final point—that the falling event rates in the statin trials matches the fall in serum lipids (see figure)—is not relevant. This apparent correlation has nothing to do with exposure–response (II). The data shown in the figure are mean values, whereas exposure–response demands a correlation between individual values. The figure is misleading, because within the trials the percentages of those suffering cardiovascular events were similar, whether the starting LDL cholesterol was high or low; this directly contradicts the hypothesis that the individual patient's LDL cholesterol, or its changes, has any importance. The HPS demonstrated, clearly, that statin treatment protected even those with a low LDL level against CHD. How can low LDL cholesterol cause coronary heart disease?

### Summary

Because Weintraub does not present convincing objections to my review, I find no reason to change my conclusions.

### References

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