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March 3, 1986

Dr. Ancel Keys
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Dear Ancel:

I have finally gotten around to respond to your article on the response of serum cholesterol or dietary cholesterol. The enclosed manuscript will apparently appear in the American Journal of Clinical Nutrition.

I have been wondering when you would question the conclusion of Mattson and Grundy that monounsaturates are as effective as the polys in lowering serum cholesterol?

Best wishes,

Sincerely,

19 March 1986

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D. M. Hegsted, Ph.D.
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Dear Mark,

Your note and copy of the ms. arrived just as we got back from five months in Italy. I appreciate having a chance to comment on this interesting ms. I enclose a copy of a letter I am sending to the Editor of Am J Clin Nutr.

Re the Mattson, Grundy piece, I enclose a copy of a letter to the Editor of J Lipid Res and of his reply. So they publish rubbish and refuse to print any comment on the fact! I shall put together a note for Am J Clin Nutr in the hope of letting other readers know how erroneous are the conclusions about oleic acid in their paper. We met in N.Y. at the Acad Med at the symposium on oleic acid and when we were through I think Fred Mattson saw the light. At least he publicly backed down about the claim for the power of oleic acid to lower the serum cholesterol level.

We are to be here in Minneapolis until early in May when we start back to Italy by way of talks in Spain.

Regards,

Ancel Keys

Serum Cholesterol Response to Dietary Cholesterol:

A Re-evaluation

by

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Running head: Serum Response to Dietary Cholesterol

Abstract

The data from the literature in which the serum cholesterol response has been measured following a change in cholesterol intake have been re-evaluated. The overall data appear to be best explained by exponential equations. However, very large differences in response have been reported for similar changes in cholesterol intake and no predictive equation can explain such values. It is concluded that over the range of cholesterol intakes of practical interest--0 to 400 mg/1000 kcal--the usual response is approximately linear, each 1 mg/1000 kcals resulting in an expected increase of serum cholesterol of approximately 0.1 mg/dl. With a 2500 kcal diet an increase in intake of 100 mg/day would be expected to increase serum cholesterol by approximately 4 mg/dl.

Key words: dietary cholesterol, serum cholesterol

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March 25, 1986

Albert I, Mendeloff, M.D., Editor
American Journal of Clinical Nutrition
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Dear Sir:

Doctor D.M. Hegsted kindly sent me a copy of a ms. he is submitting to you as a response to my Special Article: "Serum Cholesterol Response to Dietary Cholesterol." (1) My article showed that the equation published by Hegsted and colleagues (2) grossly over-predicted the effect of dietary cholesterol. The average was 300 per cent over-prediction of the serum response to change in dietary cholesterol as the only variable in 39 controlled experiments in 15 different institutions.

Dr. Hegsted now agrees that his original linear model was inappropriate because the relationship between dietary intake and serum cholesterol is actually curvilinear. From recalculation of the published date in the literature he offers an exp onential equation in which y, the change in the serum, equals 51.06 - 54.67 times e raised to the power - 0.00151 times x, the change in the cholesterol in the diet. His new equation accounts for 87.5 per cent of the variance of the serum values.The 95 per cent confidence limits of the coefficient of correlation between observed and predicted values are r = 0.89 and r = 0.97.

Twenty years ago we derived an equation based on the findings in rigidly controlled experiments in a metabolic ward. (3,4) We used the model where C, the level of cholesterol in the serum equals a + b(x to the k power) where x is the level of cholesterol in the diet. For a given person, or group of persons, we have C1 = a + b(x1) to the k power. for the same person or group on another diet differing only in cholesterol we have C2 = a +,b(x2) to the k power. By subtraction we have y = b(x1 - x2) where both x1 and x2 are raised to the k power.The best value of k to fit the data is the value of k that minimizes the square root of the sum of the squares of the differences between the observed and predicted values.

The best value of k was found by iteration over all possible values of k. That proved to be about 0.5 so it is appropriate and convenient for calculation to take the square root of x for the equation. Applying the solution with k = 0.5 to the data cited by Hegsted the 95 per cent limits of the coefficient of correlation between observed and predicted changes in the serum cholesterol are r = 0.78 and r = 0.94. Although the correlation with Hegsted´s new equation is a trifle higher the values are not significantly different.

While we applaud Hegsted´s correction of an old error, it may be suggested that his new equation is not really preferable to our old square root equation. First, there is no significant difference in the fit to the observed changes in the serum. Second, Hegsted´s new equation says that even if there is no change in dietary cholesterol or any other variable the seru8m level will change by some 3.5 mg/dl. His equation has a non-zero value for intercept. Third, Hegsted´s new equation is much less easy to use without having recourse to a computer for the calculation.

Ancel Keys

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3. Keys A, Anderson JT, Grande F. Serunm cholesterol response to changes in the diet. II. The effect of cholesterol in the diet.Metabolism 1965;13:759-65.
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Hegsted et al. data (from Table III, p. 285   26 Oct 1985

Experiments all at same total fat = 38% total calories, and same preformed dietary cholesterol intake = 306 mg./day

S' = % Cal from saturates, 12.0 thru 16.0 (no stearic or short chain sats.

M = " " " monounsats, P = % Cal from polyunsaturates.

Δ chol = y, mg/dl $\Delta S' = S_1 - S_2$, $\Delta M = M_1 - M_2$, $\Delta P = P_1 - P_2$

Period	y	ΔS'	ΔM	ΔP
1	−38.7	+4.23	+11.12	−4.15
2	+56.2	−19.24	−0.06	+7.53
3	−56.5	+3.45	+1.35	+5.87
5	−12.3	+2.92	+8.79	+1.69
6	−28.9	+4.21	+11.19	−4.98
7	+28.6	−12.73	+4.67	+6.16
18	−14.1	+3.45	+1.57	+5.87
* 19 *	−47.7	+3.11	+8.88	−16.02
20	+40.9	−6.93	+12.22	+7.68
21	−30.9	+1.62	−10.14	+3.92
23	−12.3	+0.48	+3.93	−4.83
* 24 *	−40.8	+3.18	+8.71	−17.19
25	+15.0	−12.37	+10.13	+0.28
36	+6.6	+1.62	−10.14	+3.92
N=12 mean	−3.87	−0.38	3.72	2.41
SD	34.00	8.55	7.74	4.78

*
#19 P = 24.85 % of total calories
#24 P = 26.02 % " " "

The Mattson - Grundy paper (J Lipid Res. 26, 194) 25 Oct. 1985
All diets were 40% of total energy from total fats.

Diet Fatty Acids	Type SAT % of Fat	% Cal.	Type Mono % of Fat	% of Cal	Type Poly % of Fat	% of Cal.
1) All Sats.	49.7	19.9	8.6	3.4	11.2	4.5
2) Sat excl. stearic etc.	44.4	17.8	5.8	2.3	9.7	3.9
3) Mono	40.0	16.0	73.4	29.4	14.7	5.9
4) Poly	10.1	4.0	17.9	7.2	73.3	29.3

The Minnesota Equation: CHOL is mg./dl in plasma
S and P are % of total energy of diet.

$$CHOL_1 - CHOL_2 = 2.7(S_1 - S_2) - (P_1 - P_2)$$

Comparison

	Δ CHOL mean	Observed SE	Predicted use all Sats	(using 2) no 18.0
Sat diet - Mono diet	31.1	7.1	26.6	37.6
SatO - Poly Diet	36.9	7.6	68.3	71.7
Mono - Poly Diet	5.9	5.5	55.7	34.7

So the Minnesota equation prediction for the plasma chol. difference between the values on the SAT diet and the mono diet are not different from the observed difference. Note that the effect of mono-unsaturates, as compared with equal calories of starch is zero and this calculation alone is confirmatory.
But with the enormous load of polys all goes off!