

## Reply to letters by van der Meer and Budowski

Dear Sir:

We have suggested that polyunsaturated fatty acids, unlike saturated fatty acids, are preferentially oxidized into ketone bodies in the liver rather than esterified into triglycerides. This might explain why dietary polyunsaturated fatty acids lower both serum cholesterol and triglycerides, when compared to certain saturated fatty acids (1).

Van der Meer correctly argues that in later work of the Heimberg group (2) the suppression by linoleic acid of the hepatic secretion of triglycerides (3) could not be reproduced. These problems of reproducibility might be due to the fact that in these perfusion experiments most of the triglycerides formed are not excreted but accumulate in the liver. In both experiments (2, 3) the sum of triglycerides accumulated plus triglycerides excreted after 4 h, and corrected for the fatty-acid free control, was consistently higher for livers perfused with palmitic acid than for linoleic acid (8.6 versus 6.2, and 11.8 versus 6.3  $\mu\text{mol/g}$  liver, respectively). Thus these studies consistently do suggest that palmitic acid, unlike linoleic acid, is preferentially channeled into the pathway of esterification.

Van der Meer points out that when studying the effect of unsaturation, this should be done by comparing fatty acids of the same chain length, so that linoleic acid (C 18:2) should be

compared with stearic acid (C 18:0) instead of palmitic acid (C 16:0). From the biochemical point of view this is obviously correct. However, it is essential to realize that from the nutritional point of view not all saturated fatty acids are equal. In contrast to myristic (C 14:0) and palmitic acid, stearic acid does *not* elevate the concentration of serum cholesterol (4). Thus, if our hypothesis is correct stearic acid should not inhibit ketogenesis, which indeed is shown in the Figure given by van der Meer.

Van der Meer is in error in concluding that the chain length of fatty acids does not affect ketogenesis. Even-numbered short- and medium-chain fatty acids are known to be strongly ketogenic (see letter by Budowski). However, this is not seen in the Figure (van der Meer) because in this experiment all fatty acids were added at the same molar concentration. Therefore, the amount of fatty acid carbon entering the liver was twice as high for C 16:0 as for C 8:0. If the proportion of fatty acid molecules channeled into ketone body formation were independent of chain length, then the production of ketone bodies from C 16:0 should have been twice as high as from C 8:0 in this experiment. In other words, in van der Meer's Figure the ketogenic action of caproic (C 6:0) and caprylic acid (C 8:0) is underestimated. The well-known ketogenic action of these fatty acids perfectly fits our hy-

pothesis, because medium-chain fatty acids do not increase serum cholesterol and triglyceride concentrations (4). The main saturated fatty acids affecting serum cholesterol levels are C 12:0, C 14:0, and C 16:0, which together account for at least 65% of the total saturated fatty acids in food (5). Lauric acid (C 12:0) may not affect ketone body synthesis, which would not be in agreement with its cholesterol elevating potential (4). The latter however, has been disputed (6).

Budowski is right in pointing to reports (his refs no 2 and 4) showing that in rats polyunsaturated fatty acids fed in the form of corn, sesame, and groundnut oil produce lower plasma concentrations of ketone bodies than saturated fatty acids given in the form of coconut fat and beef tallow. This would contradict our hypothesis. However, in these experiments the rats were fed essentially cholesterol-free diets. The intact rat fed such a diet is an unsuitable model for the action of various fatty acids on lipoprotein metabolism in man, because under such conditions dietary polyunsaturated fatty acids in the form of corn oil cause *higher* serum cholesterol and triglyceride levels than saturated fatty acids given as coconut fat (7, 8). The reason for this surprising but reproducible anomaly is unknown. The hypocholesterolemic effect of polyunsaturated fatty acids seen in humans is only found in rats when high-cholesterol diets are used (9, 10). It would be interesting to know the effects of different fats in high-cholesterol diets on plasma ketone bodies in rats, but the real test of our hypothesis should be in man.

Budowski also quite rightly points out that linoleic acid may be oxidized to propionyl-CoA as well as to acetyl-CoA. However, this is immaterial to our hypothesis. The essence of our suggestion was that the liver converts polyunsaturates into some form which is soluble in blood and does not require the construction of a cholesterol-containing lipoprotein vehicle for its transport. Propionate may fulfill this role just as well as acetoacetate or beta-hydroxybutyrate. According to Budowski propionyl-CoA will be converted into oxaloacetate, which will steer acetyl-CoA into the citric acid cycle instead of into the ketogenic pathway. In the fasting state, when dietary long-chain fatty acids reach the liver after having been stored temporarily in the adipose tis-

sue, the hepatic pathways of beta-oxidation and gluconeogenesis are activated. Thus linoleic acid, after having been converted first into propionate and then into oxaloacetate, is finally converted to glucose. In keeping with this suggestion, if linoleic acid was infused, the output of glucose by the perfused rat liver was significantly enhanced, compared to palmitic acid (3). However, from these experiments (3) it cannot be concluded whether the glucose carbon had been derived from linoleic acid or from endogenous sources such as glycogen or glucogenic amino acids. To summarize, if we postulate that part of the dietary polyunsaturated fatty acids do not go into the pathway of esterification and formation of very low density lipoproteins, then these molecules have to reach their final destination, ie oxidation to CO<sub>2</sub> and H<sub>2</sub>O, in peripheral tissues via some other way, which could be either the ketogenic or the gluconeogenic pathway, or both.

We have suggested that our hypothesis is easy to test by the measurement of fasting blood concentrations of ketone bodies (1). This statement may need some qualification. As suggested implicitly by van der Meer, plasma concentrations of ketone bodies are not determined solely by the rate of ketone body synthesis. The flux through the pool of ketone bodies may be more important than its size. In addition, if the formation of propionyl-CoA plays a role then this will dilute effects of polyunsaturated fatty acids on ketone body flux. What we obviously need are observations, preferably in well-controlled dietary trials with humans.

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#### References

1. Beynen AC, Katan MB. Why do polyunsaturated fatty acids lower serum cholesterol? *Am J Clin Nutr* 1985;42:560-3.

2. Wilcox HG, Dunn GD, Heimberg M. Effects of several common long chain fatty acids on the properties and lipid composition of the very low density lipoprotein secreted by the perfused rat liver. *Biochim Biophys Acta* 1975;398:39-54.
3. Kohout M, Kohoutova B, Heimberg M. The regulation of hepatic triglyceride metabolism by free fatty acids. *J Biol Chem* 1971;246:5067-74.
4. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. IV. Particular fatty acids in the diet. *Metabolism* 1965;14:776-87.
5. Katan MB, Van de Bovenkamp P, Brussaard JH. Vetzuursamenstelling, trans-vetzuur- en cholesterolgehalte van margarines en andere eetbare vetten. *Voeding* 1984;45:127-33.
6. Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr* 1965;17:281-95.
7. Kritchevsky D, Tepper SA, Bises G, Klurfeld DM. Influence of cocoa butter on cholesterol metabolism in rats: comparison with corn oil, coconut oil and palm kernel oil. *Nutr Res* 1983;3:229-36.
8. Beynen AC, Katan MB. Relations between the response of serum cholesterol to dietary cholesterol and to the type of dietary fat, protein and fiber in hypo- and hyperresponsive rats. *Nutr Rep Int* 1984;29:1369-81.
9. Alfin-Slater RB. Carbohydrate-lipid effects on cholesterol metabolism. *J Dairy Sci* 19;50:781-6.
10. O'Brien BC, Skutches CL, Henderson GR, Reiser R. Interrelated effects on food lipids on steroid metabolism in rats. *J Nutr* 1977;107:1444-54.