Effect of Dietary Fat on Synthesis and Degradation of Cholesterol by the Liver

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THE findings that the addition of unsaturated fat to the diet will lower the serum cholesterol levels of adults[1,2] and even of infants[3] have stimulated considerable work in this area, and these effects are now amply documented. How the unsaturated fat works is an important question, and the answers are still being gathered. In man there is evidence of increased excretion of cholesterol and bile acids.[4–6] A similar effect has been observed in rats, although in these animals there also appears to be increased adsorption of cholesterol.[7]

It is only natural that attention should turn to the intermediary metabolism of cholesterol under the influence of different fats. Several laboratories have investigated the biosynthesis of cholesterol as affected by dietary fat, and the results show an increased synthesis by animals fed unsaturated fat. Thus, Mukherjee and Alfin-Slater[8] compared the effects of cottonseed oil, hydrogenated coconut oil, fat-free diet and fat-free diet plus methol linoleate. Using the first diet as a control, they found that incorporation of acetate-C^{14} into rat liver cholesterol was, after sixteen weeks on the diet, 7.4, 12.2 and 100 per cent respectively for the other three diets. Wood and Migicovsky[9] compared rapeseed oil, corn oil and coconut oil and found the first two to enhance cholesterol synthesis from acetate *in vivo*. Avigan and Steinberg[10] compared coconut oil and corn oil, using both acetate-C^{14} and T_2O as substrates and found that the unsaturated diet enhanced cholesterol synthesis from either precursor. Linazasoro et al.[11] found no differences in cholesterol biosynthesis, but their feedings were carried out for three days whereas the other authors cited carried out their feedings for at least a week. They did, however, find considerably more synthesis in the fat-fed animals than in control animals kept on a fat-free diet.

Drs. Whitehouse, Staple and I have been investigating the oxidation of the terminal carbon atoms of cholesterol by the liver mitochondria of rats fed diets rich in corn oil or a commercial shortening (Crisco). Both fats were fed as 20 per cent of the diet. The preparation of the enzyme system has been described recently.[12] We find that whether we use livers of male rats, female rats or pooled livers from male and female rats, the mitochondria of the Crisco-fed rats oxidize cholesterol-26-C^{14} to $C^{14}O_2$ at a faster rate than do mitochondria from rats fed corn oil. Rats maintained on a normal diet were used as control animals. The results are summarized in Table I.

The results were consistent in each separate experiment (i.e., more oxidation with shortening than with corn oil) but the variation between experiments precludes any speculation concerning an effect of differences in sex.

Liver fat from rats on the unsaturated fat diet, when added to normal mitochondrial preparations, inhibited oxidation of cholesterol-26-C^{14} to the same extent as did liver fat from rats on the shortening diet. The

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TABLE I
Effect of Dietary Fat on Oxidation of Cholesterol-26-C^{14} by Rat Liver Mitochondria

Animals	No. Experiments	Per Cent Oxidation (Average)*		
		Control	Corn Oil	Crisco
Males	4	12.1	6.1	15.8
Females	5	8.7	7.4	14.4
Mixed	3	14.1	9.9	14.2

* All values corrected for equivalent amounts of mitochondria (mg. N).

dietary effect was not observed when the same enzyme systems were incubated with pyruvate-2-C^{14}.

We are continuing our experiments in this area in an effort to elucidate our results.

REFERENCES

1. Kinsell, L. W., Partridge, J., Boling, L., Margen, S. and Michaels, G. Dietary modifications of serum cholesterol and phospholipid levels. *J. Clin. Endocrinol.*, 12: 909, 1952.
2. Ahrens, E. H., Jr., Blankenhorn, D. H. and Tsaltas, T. T. Effect on human serum lipids of substituting plant for animal fat. *Proc. Soc. Exper. Biol. & Med.*, 86: 872, 1954.
3. Pomeranze, J., Goalwin, A. and Slobody, L. B. The effect of a corn oil–evaporated milk mixture on serum cholesterol levels in infancy. *Am. J. Dis. Child.*, 95: 622, 1958.
4. Hellman, L., Rosenfeld, R. S., Insull, W., Jr. and Ahrens, E. H., Jr. Intestinal excretion of cholesterol: a mechanism for regulation of plasma levels. *J. Clin. Invest.*, 36: 898, 1957.
5. Bronte-Stewart, B., Antonis, A., Eales, L. and Brock, J. F. Effects of feeding different fats on serum cholesterol level. *Lancet*, 1: 521, 1956.
6. Gordon, H., Lewis, B., Eales, L. and Brock, J. F. Dietary fat and cholesterol metabolism: Faecal elimination of bile acids and other lipids. *Lancet*, 2: 1299, 1957.
7. Byers, S. O. and Friedman, F. Bile acid metabolism, dietary fats and plasma cholesterol levels. *Proc. Soc. Exper. Biol. & Med.*, 98: 523, 1958.
8. Mukherjee, S. and Alfin-Slater, R. B. The effect of the nature of dietary fat on synthesis of cholesterol from acetate-1-C^{14} in rat liver slices. *Arch. Biochem.*, 73: 359, 1958.
9. Wood, J. D. and Migicovsky, B. B. The effect of dietary oils and fatty acids on cholesterol metabolism in the rat. *Canad. J. Biochem. Physiol.*, 36: 433, 1958.
10. Avigan, J. and Steinberg, D. Effects of saturated and unsaturated fat on cholesterol metabolism in the rat. *Proc. Soc. Exper. Biol. & Med.*, 97: 814, 1958.
11. Linazasoro, J. M., Hill, R., Chevallier, F. and Chaikoff, I. L. Regulation of cholesterol synthesis in the liver: The influence of dietary fats. *J. Exper. Med.*, 107: 813, 1958.
12. Whitehouse, M. W., Staple, E. and Gurin, S. Catabolism in vitro of cholesterol. I. Oxidation of the terminal methyl groups of cholesterol to carbon dioxide by rat liver preparations. *J. Biol. Chem.*, 234: 276, 1959.