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Received October 16, 1961. P.S.E.B.M., 1962, v109.

Effects of a High Cholesterol Diet on Synthesis of Plasma Low Density Lipoprotein.* (27087)

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When diets high in fat and cholesterol are fed to animals, plasma cholesterol levels are elevated. In some species, such as the rabbit, the levels reached are very high and atherosclerosis readily develops(1). Under these circumstances, the low density or β lipoprotein levels in plasma are particularly increased. It is difficult to elevate the plasma low density lipoproteins in the rat to this degree by feeding such diets, but there is no doubt that elevation of plasma and liver cholesterol content can be achieved(2). Can such diets affect the rate of hepatic synthesis of the low density lipoproteins in the rat? We have recently succeeded in measuring the net synthesis of plasma low density lipoproteins in the perfused rat liver by an immunochemical method(3) and have now applied this technic to an investigation of the effects of a high fat-high cholesterol diet. Our results indicate that, in the rat, such a diet does not lead to an increased synthesis of the protein moiety of the low density lipoproteins but does increase the amount of cholesterol present in the lipoprotein molecule released by the liver during perfusion *in vitro*.

Materials and methods. The rats used were of the Wistar strain, weighing between 270 and 300 g, and were fed for 3 weeks on a commercial "cholesterol-free" diet (Nutritional Biochemicals Corp.) containing either 15% of added Wesson oil or 15% of Wesson oil plus 5% of cholesterol. The livers were perfused for 1 hour at 37° with a suspension of rat red cells in Krebs-Ringer-bicarbonate medium as previously described(3,4) and the amount of low-density lipoprotein measured by means of the quantitative precipitin reaction with an antiserum prepared in the goat. The immune precipitate was analyzed for its cholesterol(5) and protein(6) content, thus affording a measure of the synthesis of both cholesterol and protein moieties.

Results and discussion. The results shown in Table I indicate that addition of 5% of cholesterol to the diet resulted in a 3-fold increase in amount of cholesterol in low density lipoprotein appearing in the perfusion fluid with no significant increase in amount of the protein moiety. The high cholesterol diet caused a 3-fold increase in liver cholesterol

* This work was supported by grant from Nat. Inst. Health, U.S.P.H.S.

content but only a 15% rise in plasma cholesterol (Table II). There may be several reasons why the plasma cholesterol level is not equally increased. One possibility is that the rate of removal of cholesterol from plasma lipoproteins may also be increased under these conditions in the intact animal. Furthermore, our perfusions are carried out with a red cell suspension containing no plasma protein. Re-entry of cholesterol from plasma lipoprotein into the liver may be disfavored by this perfusion system if the uptake requires a normal concentration of circulatory plasma lipoprotein.

In the rat(7) and the dog(8), feeding of a high cholesterol diet results in a depression in rate of conversion of labeled acetate to cholesterol by the liver. These experiments provide information only on the extent to which endogenous synthesis of cholesterol occurs, and do not necessarily bear any relation to the rate at which the liver is synthesizing plasma lipoprotein which contains cholesterol of either dietary or endogenous origin.

The failure of a high cholesterol diet to increase the incorporation of radioactive amino acids into the circulatory plasma lipoproteins of perfused rat livers has been reported by Haft *et al.*(9). Similar results were obtained with liver slices by Radding and Steinberg (10). The present experiments are in agreement with these results. It is interesting to contrast this situation with that in experimenal nephrosis, where there is an enormous increase in plasma low-density lipoproteins and the net synthesis of both the protein and the cholesterol moieties is likewise increased (4). Evidently, the synthesis of the protein and the lipid moieties of the plasma lipoproteins are not necessarily linked under all circumstances.

TABLE I. Net Synthesis of Low Density Plasma Lipoprotein by Perfused Livers from Control and Cholesterol-Fed Rats.

Diet fed	No. of exp.	Lipoprotein synthesis: Cholesterol moiety (μg/hr/200 g body wt)	Lipoprotein synthesis: Protein moiety (μg/hr/200 g body wt)
15% Wesson oil	4	178 ± 13.0*	850 ± 86.6
Idem + 5% cholesterol	4	533 ± 46.6†	866 ±124.8

* Stand. error of mean.
† Significantly different from mean value for the oil-fed controls ($P < .001$).

TABLE II. Comparison of Control and Cholesterol-Fed Rats.

Analysis*	Controls (oil-fed)	Cholesterol + oil-fed
Plasma cholesterol, mg/100 ml	105 †	121
Liver cholesterol, mg/g	3.93	11.65
Liver as % of body wt	3.46	3.70

* Mean of 3 rats in each group.
† These values for plasma cholesterol are higher than those ordinarily obtained in the rat. This is due to the method employed(11) which, in rat plasma, consistently gives higher results than those obtained by the Sperry-Webb procedure(5).

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Received October 23, 1961. P.S.E.B.M., 1962, v109.