ABSTRACT

1. Administration of 3-hydroxy-3-methylglutaric acid (HMG) for one week to normally-fed rabbits caused significant lowering of serum total, esterified and free cholesterol, total phospholipids and triglycerides. Serum lyssolecithin, lecithin, sphingomyelin and cephalins also decreased.

2. In hypercholesterolemic rabbits returned to a normal diet, two week's administration of HMG caused a gradual decrease in serum cholesterol and phospholipids over this period. The serum triglycerides level and aortic lipid concentrations were markedly lowered at the end of this two week's treatment. Serum cephalins and other phospholipids were also lowered in these animals.

3. Simultaneous administration of HMG and feeding the atherogenic diet for 54 days prevented the rise in serum cholesterol and phospholipid levels. Triglyceride levels in serum, liver and aorta were significantly reduced, serum cephalins substantially decreased, while cardiolipin almost disappeared. Aortic lyssolecithin, lecithin, cephalins and cardiolipin also decreased in these animals.

4. In vitro HMG caused a marked decrease in rat hepatic malic enzyme activity (35%), while NADP-isocitric dehydrogenase...
and malic dehydrogenase were significantly increased by 20 and 18%, respectively. However, HMG had no \textit{in vitro} effect on glucose-6-phosphate dehydrogenase and lactic dehydrogenase activity. Inhibition of malic enzyme seems to be allosteric both with the crude as well as partially purified enzyme preparations. The concentration of HMG required for 50% inhibition was $39.2 \times 10^{-3}$ M.

5. Administration of HMG to normally-fed rats for one week caused significant decrease in the activities of malic enzyme and glucose-6-phosphate dehydrogenase by 25 and 19%, respectively. Lactic dehydrogenase and NADP-isocitric dehydrogenase activities were also significantly increased but there was no \textit{in vivo} effect of HMG on malic dehydrogenase activity.

6. When HMG treatment was extended to 5% cholesterol-fed rats for one week, a pronounced increase in the activity of malic enzyme (85%), glucose-6-phosphate dehydrogenase (53%), lactic dehydrogenase (60%) and malic dehydrogenase (25%) was observed. However, a little but significant increase (11%) was recorded in NADP-isocitric dehydrogenase activity.

7. HMG treatment to the fasting rats (48 hr) significantly increased the activities of malic enzyme, glucose-6-phosphate
dehydrogenase and NADP-isocitric dehydrogenase by 57.42 and 15%, respectively. However, HMG had no significant effect on malic dehydrogenase and lactic dehydrogenase under these conditions.

8. In fasted (48 hr), fat free diet-refed (48 hr) rats, the activity of malic enzyme and glucose-6-phosphate dehydrogenase was increased. This increase was inhibited in HMG-treated animals by 32% in case of former and 42% in the latter. Under similar conditions HMG did not significantly affect the activities of lactic dehydrogenase, malic dehydrogenase and NADP-isocitric dehydrogenase.

9. In HMG-treated normally-fed rats, the incorporation of acetate-1-C\(^{14}\) into hepatic fatty acids was increased by 120%. This indicated an increased fatty acid synthesis. However, under these conditions malic enzyme and glucose-6-phosphate dehydrogenase activities were lowered which is an incomprehensible biochemical effect of HMG.