V. SUMMARY
Hypercholesterolemia and hyperlipidemia are prelude to atherosclerosis. 3-Hydroxy-3-methylglutaric acid, a known hypolipidemic agent for rats, also significantly decreased serum cholesterol, phospholipids and triglycerides of normally-fed rabbits. Furthermore, serum lecithin, sphingomyelin and cephalins were also lowered significantly. In hypercholesterolemic rabbits transferred to basal diet similar results were obtained in serum and aorta on HMG administration. Serum, liver and aortic cholesterol, triglycerides and phospholipids were strikingly low in HMG-treated rabbits simultaneously fed an atherogenic diet. Among serum and aorta phospholipid fractions in long-term atherogenic diet-fed rabbits cephalins were maximally lowered. The decrease observed in almost all lipid fractions strongly suggests an effect on serum lipoproteins. Among lipid parameters triglycerides were markedly decreased in all experiments suggesting an inhibition of triglycerides formation in liver and hence an effect on VLDL and LDL. Furthermore, the fall in serum triglyceride levels occurred in the absence of rise in hepatic triglyceride concentrations. Therefore, it appears that inhibition of hepatic formation of triglycerides, rather than assembly of lipoprotein complexes or their release may be the initial mechanism by which HMG inhibits triglycerides
output from liver. However, an additional effect on lipoprotein synthesis, assembly or release may not possibly be ruled out. An effect at the level of lipid absorption and degradation may be also possible. Higher concentrations of sphingomyelin and cephalins are also believed to be an index of atherogeneity. Therefore, their reduction along with other phospholipid fractions suggests a role of HMG, in addition to alleviating hyperlipemia, on the reduction of lipid deposition in aorta and other tissues.

Under varying dietary stress, in vivo and in vitro effect of HMG on hepatic enzymes clearly demonstrates its interference with fatty acid synthesis besides cholesterol and triglycerides. In vitro HMG lowered the malic enzyme activity and this inhibition seems to be allosteric with both crude and partially purified enzyme preparations. The significance of this observation is yet to be investigated with more purified enzyme. In normal-fed and in fasted-refed rats both malic enzyme and glucose-6-phosphate dehydrogenase activities were significantly lowered on HMG administration. Since malic enzyme and glucose-6-phosphate dehydrogenase are considered to be the better determinants of fatty acids synthesis, the hypolipidemic action of HMG could have been
exerted by controlling the NADPH available for lipogenesis. The in vitro and in vivo increase, observed in NADP-isocitric dehydrogenase activity, under varying dietary conditions could also be responsible for decreasing citrate concentration which in turn may diminish fatty acid synthesis through inactivation of acetyl CoA carboxylase.

In cholesterol-fed rats, HMG treatment brings about a pronounced increase in malic enzyme, glucose-6-phosphate dehydrogenase, malic dehydrogenase, lactic dehydrogenase and NADP-isocitric dehydrogenase. All these enzymes increased in fasted rats except lactic dehydrogenase and malic dehydrogenase which did not respond to HMG treatment. The increase in enzyme activities in both conditions appears to be an incomprehensible biochemical effect of HMG which lowers lipid content in blood and liver. It could, therefore, be assumed that HMG is capable of correcting the large scale starvation induced changes in internal nutrition of the animals. To explain the enhancement of malic enzyme and glucose-6-phosphate dehydrogenase activities on HMG administration in cholesterol fed rats, the possible role of degradation and synthesis of more enzyme cannot be excluded. The enhancement of acetate-incorporation into hepatic fatty acids of normally-fed rats...
is again an incomprehensible biochemical effect of HMG. The acceleration of fatty acid degradation could also be one of the possible ways to explain the hypolipidemic action of HMG.

Our studies suggest that HMG has a great potential as hypolipidemic drug; it is effective in both short and long-term administration. It coulds

(i) inhibit cholesterol synthesis and triglycerides formation and its output from liver.

(ii) inhibit lipoprotein synthesis; their assembly and reduction in their release from liver.

(iii) possibly effect on absorption and degradation of lipids.

(iv) inhibit malic enzyme in vivo as well as in vitro but glucose-phosphate dehydrogenase activity in vivo only.

(v) increase NADP-isocitric dehydrogenase activity causing less availability of citrate for acetyl CoA carboxylase activation and hence indirectly lower the rate of fatty acid synthesis.

(vi) accelerate fatty acid degradation.

(vii) possibly effect on degradation and synthesis of malic enzyme and glucose-6-phosphate dehydrogenase.