V. Summary
Drugs designed to lower circulating atherogenic lipoproteins such as VLDL and LDL or to increase the putative anti-atherogenic HDL, are used in the expectation that they will retard or even reverse the atherosclerotic process. The process of selection of new agents of this kind is usually based on assessment of their effect on circulating lipids and lipoproteins in laboratory animals. In the present work efforts have been made to show that HMG could be a promising hypolipidemic drug of future after a systematic clinical and pharmacological screening.

To investigate the mechanism of lipid lowering action of HMG, the effects of i.p. administration of HMG were studied in normolipidemic, hyperlipidemic and diabetic rats. Rats were made hyperlipidemic by feeding them fat-rich cholesterol diet. Diabetes was experimentally induced in rats by alloxan treatment (i.v.). These rats were treated (i.p.) with HMG (25.0 mg/kg body weight). Rats treated with saline served as corresponding controls in each of the experimental groups. Plasma lipids, lipoproteins, post-heparin plasma lipases, tissue myocardial and hepatic lipases were analyzed in both HMG treated and control rats. Platelet aggregation studies were also carried out.

1. Earlier observations were confirmed that HMG effectively lowers plasma lipids in both normolipidemic and hyperlipidemic rats. HMG was also found to effectively lower
plasma lipids of alloxan-induced diabetic rats.

2. Plasma lipoproteins were measured turbidimetrically and by agarose gel electrophoresis. In all the experimental groups, HMG was found to lower the levels of atherogenic lipoproteins (VLDL+LDL) and to raise the levels of HDL in plasma.

3. Analysis of the lipid parameters (cholesterol, phospholipids, triglycerides) of individual lipoproteins provided a better information about the mode of action of HMG involving its effect on lipoproteins.

4. Concentration of all the lipid parameters were decreased in a combined fraction of VLDL plus LDL, significantly, in each of the experimental group treated with HMG indicating an over all decrease of these lipoproteins.

5. VLDL-cholesterol, VLDL-phospholipids and VLDL-triglycerides were also decreased significantly. HMG treatment also resulted in a decrease of VLDL-cholesterol : VLDL-triglyceride ratio in hyperlipidemic and diabetic rats indicating a selective depletion of cholesterol in this lipoprotein fraction.

6. LDL lipids were measured indirectly based on the values of VLDL and VLDL+LDL lipids. LDL-cholesterol and LDL-triglycerides were significantly reduced. LDL-phospholipid was either decreased or remained unchanged.

7. HMG treatment resulted in a significant increase of
HDL-cholesterol in hyperlipidemic and diabetic rats and a nonsignificant increase in normolipidemic rats. HDL-triglycerides were decreased significantly in all the groups but no significant effect was observed on HDL-phospholipids.

8. A more clear information regarding the effect of HMG on HDL was drawn from the analysis of HDL subfractions. The concentration of cholesterol and phospholipids increased in HDL\textsubscript{2} subfraction. The increase was more significant in diabetic group than in hyperlipidemic group but was non-significant in normolipidemic group. Increase in HDL\textsubscript{3}-cholesterol did not show statistical significance. However, HDL\textsubscript{3}-phospholipids decreased in diabetic group and HDL\textsubscript{3}-triglycerides in hyperlipidemic group significantly. The ratio of HDL\textsubscript{2}-cholesterol : HDL\textsubscript{3}-cholesterol was higher in all the groups treated with HMG. From these observations it is inferred that among HDL subfractions, HMG has a more pronounced effect on HDL\textsubscript{2} than HDL\textsubscript{3}.

9. HMG treatment also resulted in a decrease of the indicators of atherogenic risk which are given in terms of the ratio of plasma cholesterol : HDL-cholesterol and the ratio of VLDL+LDL-cholesterol : HDL-cholesterol. The effect was more significant in hyperlipidemic and diabetic rats than normolipidemic rats.

10. Besides affecting the lipid components of lipoproteins, HMG also affected the apolipoproteins of different
lipoprotein fractions indicating that the mode of action of HMG involves its interference with the lipoprotein metabolism.

11. Lipoprotein lipase and hepatic lipase are the key enzymes involved in the metabolism of lipoproteins. HMG treatment produced an increase in the activity of these lipases. The effect was more pronounced and significant for lipoprotein lipase than for hepatic lipase.

12. Both in vivo and in vitro, HMG inhibited ADP-induced aggregation of blood platelets. The speed of aggregation as well as time for maximum aggregation also decreased in HMG treated rats.

HMG belongs to the class of lipid lowering agents which are competitive inhibitors of HMG-CoA reductase. The action of HMG appears to involve enhancement in lipoprotein lipase mediated hydrolysis of triglyceride rich lipoproteins. This process would be accompanied by an increased conversion of HDL₃ to HDL₂, which is the preferred substrate for hepatic lipase. The increase in the activity of hepatic lipase upon HMG treatment supports this view. The enhanced activity of plasma lipoprotein lipase may explain the lowering of plasma atherogenic lipoproteins in response to HMG treatment. Increase of plasma HDL by HMG was due to an increase in its HDL₂ subfraction. Since inhibition of intracellular cholesterol biosynthesis is known to enhance the expression
of receptors, responsible for the uptake of both VLDL remnants and LDL on cell surfaces, it is suggested that increased number of receptors in response to HMG treatment might have resulted into augmented removal of circulating VLDL remnants and LDL to fulfil cellular demand for cholesterol through receptor mediated endocytosis. Enhanced activity of lipoprotein lipase would then be responsible to maintain a critical intracellular cholesterol level. A model for hypolipidemic action of HMG has been proposed (Fig. 16). The effect of HMG was dependent on the physiological conditions of the animals. A more pronounced effect of HMG in diabetic rats, observed in all the investigations, has been explained in terms of higher uptake of HMG due to the alterations in membrane permeability as reported by other workers in this pathophysiological condition. HMG was capable to counteract the effects produced by diabetogenic agent alloxan. In light of these observations and the current knowledge of the role of cAMP in regulating adipose tissue lipolysis, it is suggested that, like nicotinic acid, activity of HMG is mediated through its action on adenylate cyclase. In an independent study HMG has been shown to inhibit the activity of adenylate cyclase in triton-induced diabetic rats. Inhibitory effect of HMG on platelet aggregation seems to be a secondary effect produced as a result of the alterations of lipids and lipoproteins in
plasma. Consequently this might affect the lipid composition of platelet membranes which is known to be directly influenced by the platelet environment, the blood plasma. All these effects are beneficial in the respect that they decrease the risk for coronary heart disease.