CHAPTER VII

SUMMARY
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A brief summary of the important findings is given below.

I. Effect of glucagon on the metabolism of cholesterol.

Both acute and chronic administration of glucagon caused a significant alteration in the metabolism of cholesterol in the liver. Administration of a single dose of glucagon produced decrease in the concentration of cholesterol in the serum and liver and no significant alteration in the aorta while chronic administration of the hormone caused lowering of serum cholesterol, increase in liver cholesterol and no significant alteration in the aortic cholesterol. Triglycerides decreased in the serum, liver and aorta except in the case of chronic administration in the aorta.

Concentration of cholesterol in the serum HDL fraction though not significantly altered on acute administration of the hormone decreased significantly on chronic administration. However, the concentration of cholesterol in the LDL + VLDL fraction decreased significantly both on acute and chronic administration.
Both acute and chronic administration of the hormone decreased significantly the activity of HMG CoA reductase in the liver. Incorporation of $^{14}$C acetate into liver cholesterol was depressed on administration of a single dose of the hormone, but there was no significant alteration on chronic administration.

Concentration of total bile acids in the liver was increased on acute administration of the hormone and decreased on chronic administration.

Release of lipoproteins into the circulation was significantly depressed both on acute and chronic administration of the hormone.

The activity of lipoprotein lipase in the adipose tissue was not significantly altered on acute administration of the hormone but increased on chronic administration.

There was decreased concentration of ester cholesterol in the liver and serum both on acute and chronic administration of the hormone.

Thus the results obtained indicate that acute administration of the hormone causes decreased cholesterologenesis in the liver (as evidenced by decreased activity
of HMG CoA reductase and decreased incorporation of label into liver cholesterol), increased degradation of hepatic cholesterol to bile acid (as evident from the increase in the concentration of hepatic bile acids), decreased release of lipoproteins into the circulation and decreased esterification of free cholesterol in the liver. The decrease in the concentration of liver cholesterol inspite of decreased release of lipoproteins may be due to its decreased synthesis and increased degradation to bile acids in the liver. Thus the mechanism for the hypocholesterolemic action observed on acute administration of the hormone may involve decreased synthesis of cholesterol in the liver, most of the newly synthesised cholesterol being channelled for bile acid synthesis, and less for lipoprotein synthesis. Consequently less of lipoproteins are released into the circulation.

The effect of chronic administration of the hormone eventhough producing hypocholesterolemia is different in the liver. There is increase in liver cholesterol on chronic administration. Concentration of bile acids in the liver though increased on acute administration showed decrease on chronic administration. One reason for the decrease in the degradation of cholesterol to bile acids may be that more bile acids are reabsorbed into the
enterohepatic circulation as is evident from the decrease in the fecal excretion of bile acid on chronic administration of the hormone. It is known that the degradation of cholesterol to bile acids in the liver is influenced by the concentration of bile acids returning to the liver in the enterohepatic circulation. Most of the bile acids are absorbed by an active transport mechanism in the terminal ileum and taken back to the liver where they (particularly cholic acid) inhibit, by feedback inhibition, cholesterol-7α-hydroxylase which catalyses the rate-limiting step in cholesterol degradation. The decreased fecal excretion of bile acid caused by chronic administration of the hormone indicates increased absorption of bile acid into enterohepatic circulation resulting in more bile acids reaching the liver. This would result in inhibition of bile acid synthesis even though the hormone by itself may stimulate hepatic degradation of cholesterol as is evident from the acute effect.

Eventhough HMG CoA reductase activity in liver decreased on chronic administration of the hormone, cholesterol synthesis is not altered in the liver. The increase in liver cholesterol may be due to less degradation of cholesterol to bile acids and less utilization of the cholesterol for lipoprotein synthesis.
II. Effect of glucagon on the metabolism of glycosaminoglycans

The results obtained indicate that administration of glucagon for seven days produced significant alteration in the metabolism of glycosaminoglycans in the liver. The concentration of total glycosaminoglycans decreased in the rats administered the hormone. All the individual glycosaminoglycan fractions except heparin showed significant decrease while concentration of heparin was not significantly altered.

Activity of enzymes involved in the biosynthesis of precursors of glycosaminoglycans namely glucosamine-6-phosphate isomerase and UDP glucose dehydrogenase was not affected by the hormone.

The activity of enzymes involved in the degradation of glycosaminoglycans namely β-glucuronidase, β-N-acetyl-glucosaminidase, hyaluronoglucosaminidase, aryl sulfatase and cathepsin-D all decreased significantly in the liver on administration of the hormone.

Sulphate metabolism in the liver was also significantly altered by the hormone. The concentration of PAPS decreased in the liver on administration of the hormone.
The activity of sulphate activating system (which includes sulphate adenylyl transferase and adenylyl sulphate kinase) and that of sulfotransferase decreased.

The decrease in the concentration of glycosaminoglycans observed in the liver on administration of the hormone may be due to their increased degradation.

III. Effect of glucagon on the metabolism of glycoproteins.

Administration of glucagon for seven days resulted in significant alteration in the metabolism of glycoproteins in the liver. The concentration of total hexose, fucose and sialic acid decreased significantly in the rats administered the hormone.

The activity of glycohydrolases studied, namely, β-galactosidase, β-glucosidase, β-fucosidase and β-N-acetyl hexosaminidase showed significant increase on administration of glucagon.

The decrease in the concentration of carbohydrate components of liver glycoproteins may be due to the increased activity of glycohydrolases.

IV. Effect of glucagon on the metabolism of collagen and elastin.

Administration of glucagon resulted in increase in the concentration of total and insoluble collagen in the liver whereas the concentration of soluble collagen decreased. Concentration of elastin increased in the liver in the rats administered glucagon.