CHAPTER I

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In recent past, mankind has achieved a flattering record in the control of many diseases resulting in the reduction of mortality and morbidity. However, coronary heart disease and atherosclerosis are the outstanding exceptions in this general picture. Interestingly, these diseases cpntinue to be the foremost factors in overall diabetic morbidity and mortality (Robertson and Strong, 1968). One of the chief objectives of the treatment of diabetes is to minimize or prevent the development of its complications. The present day treatment effectively prevents its acute complications like ketoacidosis or infections but the same can not be said about the vascular complications of diabetes.

All agree that insulin is essential for those who have classical symptoms and ketonuria. However, the value of treating asymptomatic, nonketotic patients with insulin or oral hypoglycaemic agents is disputed by some. Hyperglycaemia, no doubt, is an important manifestation of the disease but it is neither the 'primary' nor the 'essential' one. Metabolic derangements in diabetes are not confined to carbohydrates only but include fats, proteins and electrolytes as well. Similarly, abnormalities of lipid and carbohydrate metabolism are

commonly found in patients with atherosclerotic vascular disease.

Since lipid is the major component of the atheromatous plaque, several studies have attacked lipid metabolism in relation to development of vascular complications. Serum lipoprotein patterns and estimation of cholesterol triglycerides and free fatty acids are of great diagnostic value in the study of diabetes and its vascular complications. The relevance of hypertriglyceridaemia to the development of atherosclerosis was first suggested by Albrink and Man (1959). This was further confirmed by the presence of endogenous hypertriglyceridaemia in a large proportion of cases associated with disturbances of carbohydrate metabolism and the decreased activity of the fibrinolytic system leading to atherosclerosis (Brown et al 1965; Glueck et al 1969; Spottle et al 1970 and Holzknecht et al 1970). Recently, a ten year long term study in Stockholm by Carlson and Bottinger (1972) has also shown excess morbidity and mortality in subjects with raised plasma triglyceride concentration. Epidemiological studies in Cape town by Prof.J.F.Brock were of fundamental importance in relation to the role of cholesterol (Bronte—Stewart et al 1955)

whereas the significance of hypertriglyceridaemia was first defined by Dr.Arnold Antónis (Antonis and Brockner 1960).

Studies in diabetic individuals show that those who maintained good control from the time diabetes was diagnosed were the ones who suffered much later and with less frequency and severity from vascular diseases (Lundback 1953; Skouby 1956; Hardin et al 1956; Johnson 1960 and Marble 1971). There are other studies which show that severity and frequency of vascular disease is not related to control of diabetes as much as to the therapy (Danowski 1957; Vaishnava et al 1968 and Raheja et al 1970). Knowles (1970) who critically scrutinized 85 studies found no evidence to show the beneficial effect of good control. It is therefore pertinent to observe the long term effects of therapy in relation to the complications of diabetes.

Diabetes mellitus is treated by diet alone or with oral hypoglycaemic drugs or insulin. Oral anti-diabetic drugs belong to either sulfonylurea group or biguanide class. Sulfonylurea compounds act by stimulating the release of insulin from pancreas and by potentiating the action of insulin on liver and peripheral tissues. The mechanism by which insulin release is induced is not

clear. Excessive hypoglycaemia is frequently observed in patients taking this type of drug. Sulfonylureas commonly used are tolbutamide, chlorpropamide, acetohexamide, tolazamide and a few others. Of the new sulfonylureas drugs undergoing clinical trials, glibenclamide (glyburide, HB 419) or "Daonil" appears to be more promising with respect to the effectiveness and low toxicity effects. Biguanide compounds presently available in the market are phenformin (DBI), butformin and metformin. The hypoglycaemic activity of the biguanides is independent of the pancreas. Combinations of biguanides and sulfonylureas are also found effective in the treatment of diabetes. Recently many studies have shown that good control of hyperglycaemia through oral drugs and insulin may not have its desired effect on the vascular disease. Most important one is UGDP (University Group of Diabetes Programme) study in which greater cardiovascular mortality was observed in diabetes treated with tolbutamide (UGDP 1970). The UGDP also had similar observations with phenformin (Knatterud et al 1971). Several studies have supported UGDP findings (Boyle et al 1972; Hadden et al 1972, Garcia 1972). Increased frequency of myocardial infarction in female patients on tolbutamide was also noted by

Baldimos et al (1967) but they attributed it to the higher age of their patients. They also found a rise in mean cholesterol level in their female patients treated with insulin or tolbutamide. Another report from Joslin Clinic shows greater frequency of peripheral vascular disease in the insulin treated group than in those treated with sulfonylurea or diet alone but this was attributed by the authors to greater severity of the disease. It also shows highest incidence of nephropathy in insulin treated group (Baldimos et al 1968). On the other hand, biguanides have been reported to lower the blood lipids in diabetics (Schwartz et al 1966; Alterman and Lopez Gomez 1968; Gershberg et al 1968). Thus one can clearly see the association of the serum lipids with diabetes, its vascular complications and its therapy with oral drugs and insulin. In this connection, data available on Indian subjects are very meager.

Abnormalities in insulin secretion such as raised insulin responses to oral carbohydrates are often described in patients with ischaemic heart disease (Nikkila 1965; Peter and Hales 1965), hypertension (Welborn et al 1966) and obesity (Mathews 1954; Karam et al 1963) and also in woman taking oral contraceptives (Spellacy et al 1968;

Yens and Vela 1968). Szanto and Yudkin (1969) have shown a link between sugar ingestion, hyperinsulinism, over weight and platlet function which could lead to cardio-vascular disease. Stout and Vallance Owen (1969) have suggested that hyperinsulinism may be playing a major role in the pathogenesis of atherosclerosis via insulin stimulated lipogenesis. Hence, it may be interesting to study the exact mode of action of insulin on atherosclerosis as well as lipid metabolism.

Since insulin is the driving force in the synthesis of macromolecules, change in the level of this hormone may cause metabolic alterations, acute tissue damage and various complications. Insulin regulates the activity of several enzymes. Since sulfonylureas stimulate insulin secretion, it would be worthwhile to study the enzymes which play role in lipid synthesis after long term administration of these drugs.

Very little work has been done in these lines on Indian diabetic subjects though as mentioned earlier. Raheja (1970) found that in Indian patients the control of hyperglycaemia had no beneficial effect on the occurrence of cardiovascular diseases and that those on insulin or sulfonylureas or both fared poorly as compared to those

who did not receive these drugs. However, the major drawback in most of the studies of this kind (associated with lipid metabolism) is the nonuniformity in the degree of control of diabetes in the subjects studied. In experimental animals, the glycosaminoglycans in relation to atherogenesis have been studied extensively by Kurup and others.

Further research needs to be done on evaluating the effect of long term therapy used in diabetes with reference to the lipid metabolism and atherogenesis. This may rationalize our therapeutic approach for betterment of health, well being and longer life of an Indian diabetic.

Present study :

The present study was undertaken with the following aims and objectives.

1. To study the effect of certain antidiabetic drugs on serum lipid profile (lipoprotein pattern, serum triglycerides, phospholipids and cholesterol) in well controlled Indian male diabetics treated with diet or oral drugs (tolbutamide, chlorpropamide, phenformin and combination of chlorpropamide and phenformin) and to compare the same with the lipid profiles of freshly detected untreated diabetics and normal subjects.

2. To make controlled studies on the effect of insulin and tolbutamide on lipid metabolism and in relation to atherosclerosis in normal rabbits.

3. To study the histopathological changes in various tissues such as liver, aorta and kidneys of rabbits after prolonged administration of insulin and tolbutamide.

4. To study the effect of insulin and tolbutamide on enzymes of serum and liver associated with the lipogenesis in rabbits.

5. To study the above mentioned effects of insulin and tolbutamide together with cholesterol induced atherosclerosis.

Plan of the present study :

The present study has been planned and conducted in the light of the current knowledge and existing controversies regarding the action of oral hypoglycaemic agents and insulin on lipid metabolism.

First part of the study was undertaken to examine the complete lipid profile in controlled diabetics who have been treated with tolbutamide, chlorpropamide, phenformin or combination of phenformin and tolbutamide or chlorpropamide. Diabetics treated by diet alone and untreated diabetics were also studied

in order to understand difference between drug treated diabetics and diabetics who have not received any drug. Attempt was made to collect samples from insulin treated diabetics. However, it was extremely difficult to find well controlled insulin dependent diabetic patients and hence this group could not be included. It may be noted that the duration of treatment was kept constant in all the cases (between 1 and 5 years).

The study was further extended to animal experiments. To explore the long term effect of insulin and tolbutamide on lipid metabolism, experiments were planned on normal adult rabbits receiving these drugs alone and with cholesterol. Complete lipid profile in serum, liver and aorta was studied and histopathological examination was also carried out. This way absolute atherogenic effect of insulin and tolbutamide in a nondiabetic rabbit could be studied.

A part of study was also designed to assess the activity of certain enzymes which play key role in lipogenesis in drug treated groups.

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