3) OBJECTIVE

In spite of the availability of many animal models for type 2 diabetes mellitus including genetic and chemically induced, many of them do not simulate human type 2 diabetes mellitus i.e. the pattern of disease initiation and development of it (from insulin resistance to pancreatic β cell dysfunction) do not appear same as in humans.

However, there are certain Genetic models namely Zucker diabetic fatty (ZDF) rat and db/db mouse which develop diabetes spontaneously resembling human type 2 diabetes, but these animals have following disadvantages:

- Highly inbred, homogenous and mostly monogenic inheritance and development of diabetes is highly genetically determined unlike heterogeneity seen in humans, therefore the observations derived from these highly inbred genetic strains may not always be satisfactorily extended to the human population as a whole.
- Limited availability and expensive for the diabetes study.

Further in case of a Diet /Nutrition induced diabetic animals, disadvantages are:

- Mostly require long period of dietary treatment.
- No frank hyperglycaemia develops upon simple dietary treatment in genetically normal animals and hence become not suitable for screening antidiabetic agents on circulating glucose parameter.

In Chemical induced diabetic models, Disadvantages remains continue like,

- Most of the animals (adult or neonates), requires relatively high dose of streptozotocin (STZ ; ≥ 50 mg kg⁻¹) or alloxan.
- Hyperglycemia develops primarily by direct cytotoxic action on the β cells and insulin deficiency rather than consequence of insulin resistance.
- Diabetes induced by chemicals is mostly less stable and at times reversible because of the spontaneous regeneration of β cells. Hence, care must be taken to assess the pancreatic β cell function during long-term experiments.

Also in Surgical diabetic animals problem remains like,

- Involvement of cumbersome technical and post operative procedures.
- Occurrence of some other digestive problems (as a result of part of excision of exocrine portion (deficiency of amylase enzyme).
- Dissection of alpha islets (glucagon secreting cells) too along with β cells leading to problems in counter regulatory response to hypoglycaemia.
Transgenic/knock out diabetic animals requires highly sophisticated and costly procedure for the production and maintenance therefore they are very expensive for regular screening experiments.

Therefore present research is aimed to develop ideal animal models for type 2 diabetes either by way of modification of the existing methods or by developing new methodologies or a combination of both.

The steroid dexamethasone has been shown to cause insulin resistance and diabetes (Aleksey et al 2006). Also fructose, sucrose and alloxan were found to be diabetic inducers. High fat diet produces the obesity which is also linked to insulin resistance (Blaak et al 2003).

So the objectives of present study are:

- Development of a new models in rodents for type 2 diabetes mellitus by combination of high-fat diet (HFD) and dexamethasone;
- Also by combination of HFD and fructose, sucrose, alloxan or by some other diabetic inducers.
- Model should simulate the common manifestation of metabolic abnormalities and resembles the natural history (from insulin resistance to β cell dysfunction) of type 2 diabetes mellitus in human population.
- Also the models should be easily attainable, inexpensive and useful for the investigation and preclinical screening of various compounds for the treatment of type 2 diabetes mellitus.

If proposed model/s come in existence then this model with the involvement of both insulin resistance and obvious β cell dysfunction (as in case of humans) in the development of diabetes will be suitable for studying the pathophysiology of type 2 diabetes mellitus as well as for testing new compounds. So by using this model, pharmacological screening of many drugs for their antidiabetic potential can be carried out. Also some of the complications of type 2 diabetes mellitus can be seen in this model.