AIMS AND OBJECTIVES
What should be uppermost in the mind of a clinician or a researcher in the context of any human disease? Obviously the patient’s interest: maximum relief in the shortest time with minimal drug doses and no adverse effects or discomfort to the patient. This depends on: i) a clear understanding of the underlying mechanisms of the disease and ii) a rational therapeutic strategy with mechanism-based approach to drug development and usage. In case of epilepsy the aims would, therefore be, maximal seizure control with minimal risk of disease-associated or iatrogenic ill effects. The crucial questions are:

- What is the present status of our understanding and management of epilepsy?
- Is our understanding of the underlying molecular/neurotransmitter mechanisms complete (or adequate) to deal with the problem?
- Do the available antiepileptic drugs (AEDs) provide effective seizure control without compromising with patient’s comfort?
- Is cognitive deficit an essential evil associated with the disease and its drug therapy?

Unfortunately there are no satisfactory answers to these disturbing questions at the present state of knowledge. This is a serious matter because epilepsy is one of the most common neurological disorders with an estimated prevalence of 50 million people worldwide. It is especially of concern to us as the reported incidence in developing countries is much higher (0.25 - 1.5%) than in developed countries (0.031 - 0.057%). This study, therefore, addresses the above mentioned questions and attempts to provide some approaches towards their possible solutions.
AIMS AND OBJECTIVES

- To confirm the cognitive deficits associated with the disease and its treatment by studying the ill-effects on cognitive function in experimental models for a) known seizure-inducing agents, and b) AEDs: conventional and new generation.

- To elucidate the possible involvement of histaminergic mechanisms in seizures and in the therapeutic and cognitive effects of AEDs by measuring histamine levels in various brain regions. While GABAergic and glutamatergic neurotransmission have been extensively probed as paradigms of inhibitory and excitatory elements of CNS activity, a central histaminergic neuronal system has not received the attention it deserves. There are indications that this approach might well be very rewarding.

- To develop mechanism-based AEDs exploring the use of H_3-receptor ligands for therapeutic benefit.

- To explore novel polypharmacy by studying AED combinations with: a) H_3-receptor antagonists and b) some nootropic agents for enhancing seizure control and/or reducing adverse effects.

- To probe into the mechanisms involved in the signal transduction at H_3-receptors by studying the alterations in intracellular calcium concentrations in the brain synaptosomes.
The inhibitory (passive) avoidance task in mice was chosen to study cognitive function for several reasons. Firstly, its rapid acquisition (seconds) facilitates the analysis of the time of occurrence of post-training events. Secondly, the pharmacological and molecular basis of this task have been extensively studied. Thirdly, unlike multi-trial tasks, it permits a discrimination between the pharmacology of immediate, short-term memory (STM) and that of long-term memory (LTM). Finally, it has been reliably shown to depend on the actual inhibition of one particular response (stepping down with the four paws on the grid) and not of others (like rearing, exploration etc). Our main method of study was to test the animal twice: first at 2h from training, in order to measure STM and then again at 24h, in order to measure LTM. Our choice of studying spontaneous alternation behavior, in addition to avoidance behavior, was that the former is a natural phenomenon exhibited by the rodents, is non-invasive i.e. it measures memory without the influence of shock or other stimuli, is incredibly simple to perform, is reliable and can measure spatial memory. To establish the relevance and authenticity of the experimental models used, the study envisages a probe into the possible involvement of locomotor activity on the passive avoidance test for evaluation of cognitive function.

MES and PTZ were chosen to induce convulsions because of their simplicity, reliability, ease of expressing results, the shorter time needed to produce convulsions and because of their high predictive validity. MES and PTZ are probably the best validated tests that predict drugs effective in generalized tonic-clonic (grandmal) seizures and clonic (petitmal) seizures respectively.