Preface

Attempts towards modernisation and urbanisation of the present society have pushed human beings in a very complex environment where exposure to natural and synthetic chemicals has posed a serious health problem. Besides skin and lungs, gastrointestinal tract is the major portal of entry to these foreign chemicals of non-nutritional value called xenobiotics. Intestine has long been considered as a significantly poor organ in the metabolism of xenobiotics and was simply thought to help in the transport of xenobiotics to the systemic circulation. It is only in the last fifties that the recognition of the importance of the gastrointestinal tract in disposition of foreign chemicals and drugs began appearing because of growing concern due to high incidence of cancer in the GI tract. Xenobiotics are considered potentially toxic if the body is deficient in specific biological mechanisms to deal efficiently with these compounds. The purpose of this study is, therefore, to understand such mechanisms, i.e. the drug metabolizing potentials of the intestinal epithelial cells and their use to obtain meaningful information in our understanding of chemical interactions with xenobiotics, as the epithelial cells of the entire villus-crypt surface of the small intestine are primarily exposed to xenobiotics and thus might be affected by these chemicals.

The intestinal mucosa has been shown to possess enzyme systems capable of various types of biotransformation of
xenobiotics. During this process some chemically reactive metabolites of certain xenobiotics may be formed which would react with the important biological molecules of the cell and exercise their harmful effects. The chemical interaction due to these enzyme systems can be modulated by various compounds which might increase or decrease the concentration of the parent compound in situ thereby enhancing or minimizing the chances of exposure to risk. This, understandably, demands search for a safer and non-toxic inhibitor of drug metabolizing enzymes.

Further much of the information available on the xenobiotic metabolizing potentials of the intestine is based on isolated microsomal fraction while the information on the quantitation, localization and characterization of this enzyme system and its differential sensitivity towards xenobiotics in intestinal epithelial cells along the villus-crypt surface is very limited. This, particularly, is more important in view of very high proliferating activity of crypt cells which consequently may be more prone to certain xenobiotics in causing biochemical lesions. It, therefore, requires to determine the drug biotransforming potentials of these cells which henceforth may find use in the assessment of harmful nature of xenobiotics and in understanding factors which modulate xenobiotics biotransformation in vitro and predict their in vivo effects.

The present dissertation embodies the results of some of these studies with intestinal cells of rats and guinea pigs. These studies have provided data on the basis of which many of
the earlier findings could be meaningfully interpreted and new experiments designed for attaining the ultimate objectives of clear molecular mechanism of intestinal toxicity, and for using these cells in vitro for predicting in vivo effects of chemicals and drugs.