INTRODUCTION
Desensitization, tolerance, refractoriness and tachyphylaxis are all different terms used to denote a state of diminished responsiveness of a tissue or organ that follows its prior exposure to an agonist, a hormone or a drug (Lefkowitz et al., 1980). Desensitization is known to occur with beta adrenoceptor system. Over the last few years much work has been carried out to unravel the molecular mechanisms involved in beta adrenoceptor desensitization. From this work has come an appreciation of the diversity of mechanisms that may lead to desensitization. In some cases the desensitization is homologous and only responsiveness to beta adrenergic catecholamines is attenuated. In other cases the beta adrenergic refractoriness may be part of a more heterologous picture of desensitization in which hormonal responsiveness to a variety of receptor mediated responses is affected. Homologous desensitization may indicate a receptor specific lesion whereas heterologous desensitization may be mediated at post receptor levels (Stiles et al., 1984).

Beta adrenoceptor agonists are widely used as bronchodilators since the time epinephrine was introduced as bronchodilator in England by Mathew in 1909 and in Germany by Epheraim in 1910. Isoproterenol was synthesized by Konzett in 1940 and was the first adrenergic agonist without significant alpha adrenergic activity. However, with the discovery of the beta-2 selective agonists salbutamol (Brittain et al., 1968) and terbutaline (Bergman et al., 1969), the non-selective beta adrenergic agonist isoproterenol was replaced by these drugs in the treatment of bronchial asthma.

Another important advancement in the treatment of bronchial asthma was the development in the 1960s of pressurised aerosols which could deliver precisely metered doses of bronchodilators suspended in microfine crystalline form in freon
propellents. As these devices were very convenient they were very well accepted by both physicians and patients alike. This led to increased use of adrenergic aerosol preparations in the treatment of bronchial asthma.

In 1968, the attention of physicians and pharmacologists was drawn by a publication of Spiezer and his group that with the introduction of pressurised aerosols, the asthma mortality in England and Wales rose in the patients in the age group of 5 - 34 years, the highest mortality being in the age group of 10-14 years. It was also observed that 83% of these patients had used pressurised aerosols. Several patients were found dead with empty aerosol canister besides them.

This increased mortality in bronchial asthma patients led to a wide debate on the function of beta adrenoceptors in asthma and the role of drugs in modulating the function of the beta adrenoceptor. Some scientists like Szentivanyi (1968) argued that there is a primary defect in the beta receptors of asthmatics. He showed experimentally that when guinea-pigs were sensitized with B.pertussis vaccine there was apparent reduction in the beta adrenoceptor responses. Another group (Conolly & Greenacre 1977) argued that reduced responsiveness seen in asthmatics is not a primary defect as suggested by Szentivanyi (1968) but is the result of prolonged exposure to beta adrenergic bronchodilators. They studied the lymphocyte beta adrenoceptor function and found marked depression of cyclic AMP responses to isoproterenol in asthmatics using adrenergic drugs, but not in asthmatics of comparable severity who were exclusively treated with nonadrenergic drugs like cromolyn sodium or beclamethasone. Further, asthmatics weaned off their adrenergic drugs reverted back to their normal pattern of response. On the other hand obstetric patients, who were showing normal response previously showed...
marked attenuation of lymphocyte cyclic AMP response after 48 hours of beta agonist infusion to control premature labour. These observations were followed by many experimental and clinical investigation to elucidate the molecular mechanisms involved in the process of desensitization.

The current view is that the mechanism of desensitization may involve (1) loss of affinity of the beta adrenoceptor agonist to the receptor (Lin et al., 1977; Avner & Noland, 1978) (2) down regulation of receptors (Harden et al., 1980) and (3) variation of receptor turnover (Raaka & Samuels, 1981). According to Stiles et al (1984), desensitization in a number of systems is a two step process. The immediate reaction which occurs within minutes of exposure to low concentration of isoproterenol is an uncoupling of the receptor which is not associated with reduction in receptor number and is rapidly reversed as soon as the drug is removed. The second process occurs with more prolonged exposures or a brief exposure to a higher concentration of the drug. This is not readily reversible and is associated with loss of receptors (down regulation).

Clinical studies indicate that glucocorticoids restore airway responsiveness to beta agonists in some patients who are refractory to their bronchodilator effect. (Ellui-Micaleff & Fenech 1975 ; Tattersfield & Holgate 1976 ; Svedmyir 1990 and Qing et al , 1992 ). In another experimental study in dogs Stephan et al (1980) showed that pretreatment of the animals with large doses of methyl prednisolone could prevent loss of responsiveness to isoproterenol. Glucocorticoids have also been shown to be effective in reversing the reduced beta adrenergic responsiveness in some asthmatics (Parker & Smith 1973). It is possible that glucocorticoids facilitate the action of beta agonists in airway smooth muscle.
The involvement of prostaglandins in the desensitization of airway smooth muscle to beta agonists has been shown by Douglas et al (1977). It has also been demonstrated by Omini et al (1981) that PGE₂ is generated in isolated guinea-pig trachea relaxed by isoproterenol, an event which increased significantly after desensitization of beta adrenoceptors. This could be prevented by pretreatment of the preparation with indomethacin (Berti et al., 1982).

Treatment of bronchial asthma with a combination of theophylline and a beta adrenoceptor agonist is a common procedure (Ogilvy, 1978). The rational basis for the combination of theophylline with a beta adrenoceptor agonist is the synergism of their action on the metabolic pathway of cyclic AMP leading to an increase in intracellular cyclic AMP which appears to regulate bronchodilation and mediator release in the bronchial smooth muscle (Campbell et al., 1977). Taylor (1987) has showed that aminophylline potentiates isoproterenol induced relaxation after desensitization with isoproterenol.

In the light of the above, this study was undertaken to elucidate the mechanisms involved in desensitization of beta adrenoceptor to its agonists. The study involves (1) induction of desensitization to various beta agonists that is isoproterenol, salbutamol, and terbutaline in beta adrenoceptors of guinea-pig trachea both in vivo and in vitro (2) measurement of affinities of the beta agonists for the beta receptors of the guinea-pig trachea and (3) studying the effect of pretreatment with hydrocortisone, indomethacin and theophylline on the process of desensitization as reflected by changes in affinity.