CHAPTER IV

DISCUSSION

The fact that out-patient asthmatic treatment can be a therapeutic problem. So it is important to find drugs with maximum benefit, long duration of action, ease of administration and lack of side effects. Pressurized aerosols of beta-adrenoceptor agonists were introduced into the treatment of bronchial asthma about 20 years ago. They were effective to relieve bronchial obstruction rapidly, however, major problems with short duration of action, patient abuse and excessive side effects have limited their usefulness.

It has been disputed as to which is the most suitable respiratory function test when the effects of bronchodilators are being evaluated. In pharmacological experiments particularly, PEF has been proved to be sufficiently sensitive and reliable (Simonsson, 1963). The PEFR may be a more sensitive index than the FEV in measuring changes in airway resistance after bronchodilator therapy (Ritchie and Melb, 1962).

Hoffbrand et al (1966) suggested that the peak flowmeter provided the method of choice when a convenient portable instrument was required. Its value lied in its ability in following a patient's response to treatment than in its use as a diagnostic aid (Pickworth and Westwood, 1965). In this study, it was easy for symptomatic asthmatic patients to operate mini-Wright peak flowmeter during the attacks.

Metered-dose inhalers are convenient means of administering bronchodilator aerosols to asthmatic subjects. Orehek et al, (1976) suggested that the correct use of these inhalers was important to achieve the best improvement in ventilatory function with the bronchodilator drugs. A deep inspiration to ensure deep penetration and breath-holding to ensure good retention of particles were important. In most cases, because of poor inhalation technics, probably only a fraction of a puff was inhaled. Since the bronchodilator drugs currently available were active, airways dilatation was noticable even with minute doses. Paterson and Crompton, (1976) reported that 14% of his patients used their inhalers insufficiently.

It is aware that "a puff" is an inaccurate way of giving a drug, since a variable and small amount reached the lungs (Paterson et al, 1968). However, this is the way in which the drug may be used therapeutically, and it is realized that with patients experienced in using aerosols, there is considerable consistency in this technics. There may be some variations between patients but not in this study since the comparisons were made within the same patients.

Fenoterol is chemically derived from metaproterenol by the substitution of a p-hydroxyphenyl group for a hydrogen atom on the N-isopropyl group of metaproterenol. In vitro study, Offermeier et al (1972) have shown that this increased bulkiness of the N-substituent in fenoterol resulted in an increased selectivity for beta-2 adrenergic receptors by this adrenergic agonist, as compared to metaproterenol.

O'Donnell (1970), using isolate guinea-pig atria and trachea to evaluate relative beta agonists activities, reported that fenoterol was a selective beta-2 stimulant. However, assessment of beta agonist selectivity in vitro in one species could not be considered conclusive.

The potency and duration of effects of fenoterol metered aerosols were clearly superior to those of oral doses (Beumer, 1971). In contrast, the effects on the blood pressure and pulse rate and the symptoms of sympathetic stimulation (tachycardia, tremor) produced by the aerosols were less pronounced than those produced by oral doses.

Ruffin et al (1978) demonstrated that inhalation of 200 micrograms of fenoterol was as effective as inhalation of 400 micrograms to moderate obstruction of the airways and these were the usual doese of fenoterol given by metered-dose inhaler. This study showed the same results as found by Ruffin in that inhalation of 200 micrograms of fenoterol was effective in relief of bronchial obstruction.

Litchterfeld (1972) suggested that the time interval of 5 minutes before recording the effects of fenoterol aerosols was seemed to be the most practicable. This duration, however, was too long for fenoterol since it has been reported that the action of this drug set in after just five breaths following its inhalation. According to this study, mean percentage change in PEFR after fenoterol increased significantly in 1 minute ($p < 0.001$). It meant that fenoterol had a rapid onset of action to relieve bronchial obstruction.

Recent reports have demonstrated that fenoterol was a long-acting, relatively selective bronchodilator. Beardshaw et al (1974)

found that fenoterol produced bronchodilation lasting over 3 hours following a dose of 400 micrograms, no definite advantage was found when the drug was administered in a dose of 800 micrograms.

Benjamin (1972) also reported that significant bronchodilation lasted up to the 5th. hour following 400 micrograms aerosolized fenoterol. It was shown in this study that after 200 micrograms of fenoterol aerosol, significant bronchodilation lasted up to the 5th hour ($p < 0.001$).

In order to check that the inert propellant was devoid of activity on the bronchi, all patients in this study were given inhalations of propellant alone. The changes that occurred after inhalations at any time intervals were small, showing apparently random rose and fell. The mean changes in PEFR from basal levels laid between -6.28 to 3.4%.

It was demonstrated that blood pressure, pulse rates and electrocardiograms on fenoterol study days were not significantly different from the placebo days ($p > 0.05$). In those patients in whom a marked improvement in PEFR occurred, there was sometimes a drop in pulse rate, probably resulting from the improved ventilatory capacity.

The assessment of bronchodilator drugs posed several problems. The natural variability of asthma and of patient's response from day to day caused considerable difficulty (Hume and Gandevia, 1957). One difficulty was the spontaneous 24 hour variation in the respiratory function of asthmatic patients (Mattila and Muittari, 1966). In this

study, the experiments were commenced at the same time to minimize the difference in the spontaneous improvement of the airway resistance. Even when initial measurements were the same on different days, the patient's response would depend on whether he was improving or getting worst at the time (Pain and Read, 1963).

If one sets criteria for response in order to include a subject in a study, then one must test the subject at the time of his maximum response in order not to miss an adequate response. This is, of course, impossible since it requires continuous testing. If continuous testing is not done, the maximum response could occur between tests and will, therefore be missed (Sobol, 1978).

Furthermore, several potentially reversible factors other than bronchial muscle activity might contribute to a worsening of the asthmatic state. Among these, mucosal edema and mucosal plugging were of great importance.

Another difficulty was that the spontaneous asthmatic attack was less suitable for the study than experimentally produced bronchospasm because the severity of asthmatic attacks might vary considerably in the same patients (Beumer, 1971).

Since the selectivity of fenoterol for beta-2 adrenoreceptors was not an absolute phenomenon, but only dose-related, then if the drug was stimulating cardiac beta-1 adrenoreceptors, cardiac side effects would become less apparent at lower doses (Blackhall et al, 1976). Further studies for fenoterol would be needed to criticize

this point.

Conolly et al (1971) indicated that man and experimental animals could be made resistant to beta-adrenoceptor stimulant drugs by prolonged exposure to such agents even in low doses. The mechanism for the resistance was unknown.

Adverse reaction to aerosolized bronchodilators occurred in a few patients who sustained bronchospasm rather than bronchodilation from these agents (Staneseu and Van de Woestune, 1972). This appeared to be an idiosyncratic reaction but the patients in this study had no problems about this adverse reaction.

Bass (1970) reported that death among young people inhaling fluorocarbon propellants were due to cardiotoxicity. How it led to death, remained unknown. Postulated mechanisms included the irritation of air passages with consequent worsening of asthma. Recent finding raised the possibility as a new explanation that some of these deaths might result from cardiac arrhythmias induced by the aerosol propellants (Taylor and Harris, 1970).

"Respiratory medicamentosa" means the syndrome of daily wheezing induced, at least in part, by the daily "normal" use, as well as overuse of sympathomimetic aerosols. Two possibilities for this adverse effect of adrenergic aerosols in bronchial asthma have been proposed. The first is a local irritation of the respiratory mucosa. The second is an augmented beta-adrenergic blockade by a metabolite of isoproterenol, 3-methoxyisoprenaline (Eisenstadt and

Nicholas, 1969). Each patient had to be warned that not more than one puff should be taken and not more than half-hourly intervals. It should be stated that it is dangerous to exceed this amount (Greenberg and Pines, 1967).

Long term studies would be needed for fenoterol aerosol whether it might cause any side effects such as cardiovascular problems and "respiratory medicamentosa".