BRONCHIAL REACTIVITY IN NORMAL SUBJECTS AND PATIENTS WITH ASTHMA

by

Neil Campbell Thomson MB ChB MRCP(UK)

A Thesis submitted to University of Glasgow
for the Degree of M.D.

Research carried out in
Department of Respiratory Medicine,
Western Infirmary, Glasgow.

October 1979

CONTENTS

INDEX OF TABLES

INDEX OF FIGURES

ACKNOWLEDGEMENTS

I acknowledge with gratitude the guidance I obtained from Dr. James W. Kerr, Consultant Physician in Respiratory Medicine, Western Infirmary, Glasgow. The work described in this thesis was carried out whilst I was attached to the Department of Respiratory Medicine, Western Infirmary, initially as a research registrar, and latterly as a senior registrar in general medicine and respiratory medicine. Dr. J.W. Kerr and Dr. K.R. Patel kindly extended the facilities of the Respiratory Laboratory for physiological investigations.

I wish to thank the technicians in the Respiratory Laboratory, Western Infirmary, particularly Mrs. R. Jack who provided invaluable assistance.

The first two years of this research project were supported by Fisons Limited, Loughborough and I wish to acknowledge my debt to this pharmaceutical company. I am also indebted to all the normal subjects and patients with asthma who kindly agreed to take part in the experiments described in this thesis.

I am grateful to Mr. G. Donald and his staff in the Department of Medical Illustration, Western Infirmary, Glasgow; and to Mr. D. Boyle, Cancer Intelligence Unit, Ruchill Hospital, Glasgow for

statistical advice.

Finally, I wish to thank Mrs. Janet Buttar for her skill in preparing this manuscript.

PUBLICATIONS

Listed below are the publications and presentations based on some of the work described in this thesis.

Publications

Thomson, N.C. & Patel, K.R. (1978) Effect of dopamine on specific conductance in normals and extrinsic bronchial asthmatics. British Journal of Clinical Pharmacology, 5, 521-524.

Thomson, N.C., Patel, K.R. & Kerr, J.W. (1978) Sodium cromoglycate and ipratropium bromide in exercise-induced asthma. Thorax, 33, 694-699.

Thomson, N.C. (1979) Effect of different pharmacological agents on respiratory reflexes in normal and asthmatic subjects. Clinical Science, 56, 235-241.

Thomson, N.C. (1979) Different pharmacological agents on respiratory reflexes in normal and asthmatic subjects. In Proceedings of the Mast Cell Symposium. ed. Pepys, J. & Edwards, A.M. Turnbridge Wells : Pitiman Medical - in the press.

Thomson, N.C., Green, A.G.H. & Kerr, J.W. (1979) Effect of FPL57787 in exercise-induced asthma. Clinical Allergy - in the press.

Thomson, N.C. & Kerr, J.W. (1979) The effect of H_1 and H_2 receptor antagonists in normal and asthmatic subjects. Thorax - in the press.

Presentations

Thomson, N.C., Patel, K.R. & Kerr, J.W. The role of mediator release and vagal action in exercise-induced asthma. Scottish Thoracic Society. St. Andrews, 1978.

Thomson, N.C. Different pharmacological agents on respiratory reflexes in normal and asthmatic subjects. The Mast Cell Symposium. Davos, 1979.

Thomson, N.C. & Kerr, J.W. H_1 and H_2 receptors in bronchial asthma. British Scoiety for Allergy and Clinical Immunology. Glasgow, 1979.

Thomson, N.C. & Kerr, J.W. Inhaled H_1 and H_2 receptor antagonists in normal and asthmatic subjects. Scottish Society of Experimental Medicine. Dundee, 1979.

Thomson, N.C. Exercise-induced asthma. Royal Medico-Chirurgical Society of Glasgow. Glasgow, 1979.

SUMMARY

In experimental animals and man it has been postulated that antigen-induced bronchospasm is due to the liberation of chemical mediators from mast cells, and that these mediators may act either directly on bronchial smooth muscle or via reflex vagal pathways. In exercise-induced asthma similar mechanisms may operate, possibly following non-immunological release of chemical mediators. The pathogenic mechanism underlying the increased airway reactivity to non-specific stimuli characteristic of asthma, and the transient bronchial hyper-reactivity found in some normal subjects is unknown, although it has been suggested that these responses may be due to stimulation of vagal irritant receptors in the bronchial epithelium.

The purpose of this study was, therefore, to determine the relative importance of the direct and reflex vagal effects of various stimuli upon bronchial smooth muscle. This was investigated by examining the effects of chemical mediators, non-specific stimuli and exercise upon the airways of normal subjects and patients with asthma.

Histamine is thought to be an important primary chemical mediator released from human mast cells, while, in some species dopamine has been implicated in type I hypersensitivity. The possible sites of action of these chemical mediators

upon bronchial smooth muscle were, therefore, examined. Firstly, the effects on airflow resistance of an inhaled H_1 receptor antagonist clemastine, and an inhaled H_2 receptor antagonist cimetidine were studied in normal subjects and asthmatic patients. No significant changes in specific conductance (sGaw) were seen in normal subjects. In asthmatic patients, however, a significant increase in forced expiratory volume in 1-sec (FEV_1) occurred at 60, 90 and 120 minutes following the inhalation of clemastine, whereas inhaled cimetidine had no bronchodilator effect. Clemastine and cimetidine were then tested on histamine-induced bronchoconstriction in normal subjects and asthmatic patients. Clemastine significantly reduced the fall in sGaw in normal subjects, and FEV_1 in asthmatic patients, whereas cimetidine had no protective effect. Clemastine and the anticholinergic drug ipratropium bromide were tested on methacholine-induced bronchoconstriction in normal subjects. Ipratropium bromide, but not clemastine significantly reduced the fall in sGaw after methacholine. These results suggest that if histamine is shown to be an important mediator of immediate type hypersensitivity in human asthma, then the predominate site of action of histamine upon the airways is probably directly on bronchial smooth muscle H_1 receptors.

Specific conductance was measured before and after infused and/or inhaled dopamine in normal

subjects and patients with asthma. No significant changes in sGaw occurred in either group. The α -adrenergic receptor antagonist thymoxamine infused in combination with dopamine had no significant effect on sGaw in six asthmatic patients, thus excluding any α -adrenergic activity of dopamine masking an effect on dopamine receptors. It is concluded that dopamine had no acute effect on airflow resistance in man, and that specific dopamine receptors are unlikely to exist in human airways.

The effects of afferent and efferent vagal blockade on experimental bronchoconstriction were studied in normal subjects and patients with asthma. The anaesthetic aerosol of bupivacaine hydrochloride produced no significant changes in sGaw in normal subjects. In asthmatic patients a significant fall in sGaw occurred which was significantly reduced by prior treatment with ipratropium bromide. This precluded its use in further defining the afferent vagal component of bronchial hyperreactivity in asthmatic patients. Bupivacaine but not sodium cromoglycate or saline, abolished the cough reflex in both normal subjects and asthmatic patients. Ipratropium bromide, bupivacaine and sodium cromoglycate were tested on histamine-, methacholine-, prostaglandin F_2 α -, and cigarette smoke-induced bronchoconstriction in normal subjects. Half the normal subjects had an upper respiratory tract infection in the study involving histamine.

Ipratropium bromide partially or completely reduced the fall in sGaw after histamine, methacholine and cigarette smoke, whereas bupivacaine and sodium cromoglycate (methacholine and prostaglandin $F_2\alpha$ not tested) had no protective effect. It is concluded from these studies that neither histamine, methacholine or cigarette smoke was acting on irritant receptors and a reduction in bronchoconstrictor response after an anticholinergic drug may not necessarily indicate a reflex vagal pathway. In addition, the results do not support the postulate that sodium cromoglycate reduces the activity of lung irritant receptors.

The pathogenesis of exercise-induced asthma is unknown, but both the release of chemical mediators from mast cells and reflex bronchoconstriction secondary to stimulation of vagal irritant receptors have been postulated. The ability of anticholinergic drugs ipratropium bromide and atropine sulphate to prevent exercise-induced asthma was examined in asthmatic patients. It was found that although ipratropium bromide prevented exercise-induced asthma in some patients, high dose atropine sulphate did not inhibit exercise induced asthma in the remainder. These findings suggest that the lack of inhibition of exercise-induced asthma in some patients following anticholinergic drugs is probably not due to insufficient cholinergic blockade as has been previously suggested.

In a further experiment the effect of ipratropium bromide, sodium cromoglycate and ipratropium bromide plus sodium cromoglycate in the prevention of exercise-induced asthma was examined in patients whose main site of airflow obstruction was in small (classified non-responders) and large (classified responders) airways as assessed by maximal expiratory flow rate responses to low density gas breathing. Sodium cromoglycate, ipratropium bromide and ipratropium bromide plus sodium cromoglycate all significantly inhibited the fall in FEV_1 after exercise in responders. Ipratropium bromide had no protective effect in non-responders, unlike sodium cromoglycate and ipratropium bromide plus sodium cromoglycate. The interpretation of these findings in relation to the pathogenesis of exercise-induced asthma depends on the mode of action of sodium cromoglycate and ipratropium bromide. If sodium cromoglycate is acting by temporarily stabilizing the mast cell, so preventing mediator release, then chemical mediators may be an important factor in development of exercise-induced asthma in most extrinsic asthmatics, whereas cholinergic pathways may be relevant only in those patients in whom the main site of airflow obstruction is in the large central airways.

A new oral chromone, FPL57787, which has anti-allergic activity similar to that of sodium cromoglycate was found to significantly prevent

exercise induced asthma in asthmatic patients. Since the principal effect of FPL57787 is thought to be inhibition of mast cell degranulation this result supports the hypothesis that exercise may provoke chemical mediator release. However, the H_1 receptor antagonist clemastine was found to have no significant effect in preventing exercise induced asthma. This latter result suggests that either the release of chemical mediators from mast cells is not important in the pathogenesis of exercise induced asthma or a mediator other than histamine e.g. slow reacting substance of anaphylaxis is of more relevance, and this will require further study. Finally, the H_2 receptor antagonist cimetidine was found to significantly inhibit exercise induced asthma. The mode of action of cimetidine in this study is unknown, but it is suggested that it is probably not due to a blocking action of H_2 receptors in bronchial smooth muscle.

In conclusion these results suggest that in normal subjects and some patients with asthma reflex vagal bronchoconstriction is probably less important in the bronchial response to chemical mediators, non-specific stimuli and exercise than the direct effect of these stimuli upon the airways.

ABBREVIATIONS

The following abbreviations have been used in the text.

BTPS	body temperature, pressure, and saturated.
Cyclic AMP	adenosine 3' : 5' monophosphate.
ECF-A	eosinophil chemotactic factor of anaphylaxis.
EIA	exercise-induced asthma.
FEV_1	forced expiratory volume in one second.
FRC	functional residual capacity.
FVC	forced vital capacity.
Gaw	conductance.
h	hour.
IV	intravenous.
l	litre.
MEFV	maximal expiratory flow volume.
Min	minute.
MMEF	maximum mid-expiratory flow rates.
PAF	platelet activating factor.
PEF	peak expiratory flow.
Raw	airways resistance.

RV	residual volume.
SC	subcutaneous.
Sec	second.
sGaw	specific conductance.
SRS-A	slow releasing substance of anaphylaxis.
TLC	total lung capacity.
VC	vital capacity.
$\dot{V}_{50AIR}$	expiratory flows at 50% vital capacity breathing air.
$\dot{V}_{50He}$	expiratory flows at 50% vital capacity breathing helium.
V_{tg}	end-expiratory thoracic gas volume.

CHAPTER I

HISTORICAL REVIEW

The word asthma is derived directly from the Greek, ἆσθμα, meaning a short drawn breath or panting. The first clear description of an asthmatic attack is thought to have been made by Aretaeus the Cappadocian in the second century A.D. (see Adams, 1866). The modern concept of asthma has been attributed to the observations of Thomas Willis (1678) (see Major, 1948). He described "pneumonick" asthma which was associated with obstruction of the bronchi by thick humours, swelling of the walls and obstruction from without, while "convulsive" asthma was due to cramps of the moving fibres of the bronchi. In 1717, Sir John Floyer, who himself had asthma, published his book A Treatise of the Asthma, in which he observed that "All Violent Exercise makes the Asthmatic to breath short".

A concept of asthma as an abnormality of the nervous system was suggested by Cullen (1827), and thought by Salter (1868) to be frequently due to reflex vagal mechanisms. An alternative concept of asthma, as an allergic condition, was suggested by Meltzer in 1910, based on experiments on shocked, previously sensitized guinea-pigs. Over fifty years later, the relative importance of vagal and allergic mechanisms in asthma is still unresolved. In an endeavour to further define the role of these two mechanisms in asthma, I have examined the effects of chemical mediators, non-specific

stimuli and exercise upon the airways of normal subjects and asthmatic patients. I propose, therefore, to review the following topics which are relevant to this study: atopy and type I hypersensitivity, anatomy and function of the airways, bronchial reactivity and exercise-induced asthma.

ATOPY AND TYPE I HYPERSENSITIVITY

Atopy

A tendancy for naturally occuring sensitivity to environmental agents in subjects with a personal or family history of hay fever, asthma and eczema was first noted by Cooke and Vander Veer (1916). In 1923 Coca and Cooke introduced the term atopy to cover allergies of a familial or hereditary nature. Initially it was thought that sensitivities were not passively transferable, but in 1925 Coca and Grove utilizing the Prausnitz Küstner test showed that this kind of response could be transferred by "atopic reagin" which was heat labile, non-precipitating, specific and long lasting. This was later shown to be IgE (Ishizaka, Ishizaka & Hornbrook, 1966).

There has been reservation about the use of the term atopy (Spectors & Farr, 1976). Pepys (1975) has suggested that the term atopy should be used to describe the capacity of an individual to develop type I sensitivity to common allergens, as demonstrable by skin or serological tests, without being linked to the

presence of clinical manifestations.

The pathogenesis of atopy is unknown. Several hypothesis have been proposed which include increased mucosal permeability, IgA deficiency, defective immunological control of IgE production, and abnormalities of the mast cell (Reeves, 1977).

Reaginic Antibodies

The IgE molecule is a γ_1 glycoprotein whose molecular weight is 190.000 and consists of two light and two polypeptide chains (Ishizaka, 1975). Its ability to combine with basophils and mast cells resides in the Fc part of the molecule (Stanworth et al, 1968). The sensitizing activity of human IgE is lost after heating while the antigen binding activity remains intact (Ishizaka, Ishizaka & Menzel, 1967). The concentration of IgE in the serum is minute, the bulk being combined with receptors on basophils and mast cells with high affinity. Elevated serum concentrations of total IgE in asthma were first reported by Johansson (1967). The more allergens the patient is allergic to, the higher the total IgE value (Wide, Bennich & Johansson, 1967). The level of IgE is also raised in infections with helminth parasites.

In 1970 Parish described an IgG antibody to milk which like IgE was homocytotrophic. It differed from IgE, however, in that sensitization was for a very short time and also it was not heat sensitive. This antibody

is now termed short-term sensitizing IgG antibody (IgG-STS). The clinical importance of this antibody is at present unknown.

Type I Hypersensitivity

The mast cell is the primary target cell in immediate type tissue injury (Orange, 1973). The structural characteristics of mast cells are the numerous electron dense granules each bounded by a perigranular membrane and the villus-like projections of the cell membrane (Smith, 1963). In human lung, mast cells are rare in the mucosa, but plentiful in the sub-mucosa where they are distributed randomly without any apparent relationship to blood vessels (Brinkman, 1968). Bronchial lumen mast cells have also been demonstrated in the bronchi of rhesus monkeys, dogs (Patterson et al, 1974), and humans (Patterson et al, 1977; Ts'ao et al, 1977). In rhesus monkeys, transfer of bronchial lumen mast cells from animals with airway reactivity to antigen challenge to the bronchial lumens of animals with negative airways responses resulted in transient airway reactivity to aerosol antigen challenge (Patterson, Suszka & Harris, 1978). Patterson et al (1978) have suggested that respiratory lumen mast cells may be a major potential effector cell in IgE-mediated airway responses and also in infection, toxic and non-IgE-mediated immunological airway reactions.

Human lung and nasal polyp fragments obtained from allergic subjects release mediators of immediate

hypersensitivity after being challenged with specific antigen. Normal respiratory tissues passively sensitized with IgE also release the same mediators after challenge, (Austen & Orange, 1975). Mast cells are sensitized by the attachment of IgE antibody to the cell via the Fc region, leaving the Fab region of the antibody sufficiently unattached to enable interaction through specific sites with antigen (Stanworth et al, 1968). When IgE antibody combines with antigen a series of events takes place leading to the liberation of chemical mediators of immediate hypersensitivity. The primary mediators include histamine, slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), and platelet activating factor (PAF). These mediators exist either preformed or are newly generated and subsequently released following activation of the target cell. The chemical mediators, prostaglandin and bradykinin are considered secondary mediators, and act as modulators of the release and/or action of the primary mediators (Austen & Orange, 1975). Other mediators which may be involved in immediate type hypersensitivity in some species are dopamine and 5-hydroxytryptamine (Assem, 1976). Dopamine has been found in significant amounts in the lungs of ruminants and this lung dopamine has been located in the mast cells. It is released from isolated calf lung sensitized with horse serum by compound 48/80 and by specific antigen, which suggests that, at least in this species, it may be important in immediate type allergy (Eyre & Deline, 1971). Serotonin (5-hydroxytryptamine) is not found in human or

canine mast cells (Austen, 1971), although PAF might cause release of serotonin from platelets in allergic asthma which could sensitize bronchial smooth muscle (Hahn et al, 1978).

The possible functional inter-relationships of these chemical mediators are unknown. Histamine and SRS-A potentiate one another in bronchial smooth muscle strips (Brocklehurst, 1962). In vivo histamine is known to alter venular permeability, to constrict bronchial smooth muscle and to stimulate the irritant receptor (Austen & Orange, 1975). SRS-A in vivo contracts smooth muscle, enhances vascular permeability, and decreases pulmonary compliance (Austen & Orange, 1975). The exact functional properties of PAF in vivo are unknown. ECF-A, attracts eosinophils which contain histaminase to inactivate histamine, arylsulfatase B to inactivate SRS-A, and phospholipase D to inactivate PAF. Histamine may have an inhibitory effect on mediator release by elevating cellular adenosine 3' : 5' monophosphate (cyclic AMP) via an H_2 receptor (Lichtenstein, 1973). It is unlikely, however, that the release of type I mediators alone can be solely responsible for subacute or chronic asthma.

ANATOMY AND FUNCTION OF THE AIRWAYS

General Structure

The airways consist of a series of branching tubes which become narrower, shorter and more numerous as they penetrate into the lung. The trachea branches into

right and left main bronchi and these then subdivide into lobar bronchi, segmental bronchi and so on for 27 generations. The first 19 generations make up the conducting airways, which contain no alveoli and therefore take no part in gas exchange. The terminal bronchioles divide into respiratory bronchioles, then into alveolar ducts both with alveoli budding from their walls. This alveolated region is known as the respiratory zone and is where gas exchange occurs.

Bronchial smooth muscle extends from the trachea down to the alveolar ducts (Widdicombe & Sterling, 1970). In the trachea and main bronchi there is a C shaped cartilaginous support and the smooth muscle is arranged horizontally being attached to the inner aspects of the cartilage. The diameter of these bronchi are reduced by smooth muscle contraction. In the medium and smaller sized bronchi, the muscular attachment to cartilage disappears and the direction of the fibres becomes more oblique; contraction reduces both the calibre and the length of the airways. The mass of muscle in proportion to the diameter of the airways increases in the more distal airways (Widdicombe, 1963). Thus smooth muscle contraction in these airways produces a far greater proportional decrease in the diameter of the smaller than larger airways (Widdicombe, 1963).

The large airways are lined by ciliated pseudo-stratified columnar epithelium resting on a basement membrane. There are numerous goblet cells and the

lamina propria consists of a small amount of reticular and collagenous connective tissue and many elastic fibres. Submucosal glands are found in airways with cartilage in their wall, more abundantly in the larger rather than the smaller bronchi. Mast cells are plentiful in the submucosa and have also been demonstrated in the bronchial lumen of rhesus monkeys, dogs (Patterson et al, 1974) and humans (Patterson et al, 1977; Ts'ao et al, 1977).

The pulmonary arteries branch alongside the airways but branch more frequently than the airways. They supply blood to the capillary network of the terminal respiratory units. Supernumery pulmonary arteries pass into the periphery of an acinus. The bronchial arteries run in the airway walls supplying the capillary bed of the airway wall from hilum to terminal bronchiolus. The pulmonary veins drain all intrapulmonary structures and have no fixed relation to the airways.

Innervation of the Lung

Parasympathetic and sympathetic nerve fibres reach the lungs through the anterior and posterior pulmonary plexuses formed by branches of the vagus and the sympathetic. Within the lung the nerves are grouped in peribronchial and periarterial plexuses. The main motor innervation of airway smooth muscle comes from the vagus nerve. In both monkey and dog, dense cholinergic innervation has been shown using a specific histochemical

stain acetyl cholinesterase (Fillenz, 1970; El-Bermani & Grant, 1975). Normal airways tone is maintained by vagal efferent nervous activity which can be abolished by anticholinergic drugs (Olsen et al, 1965) and by vagotomy (Widdicombe, Kent & Nadel, 1962). Electrical stimulation of the vagus nerves causes broncho-constriction. In the absence of vagal tone, electrical stimulation of the thoracic sympathetic nerves has no significant effect on airways calibre (Cabezas, Graf & Nadel, 1971). Richardson & Beland (1976) have suggested that no adrenergic nerves are present in human airways smooth muscle, although these nerves can be demonstrated in other species. The significance of a respiratory non-adrenergic inhibitory nervous system (i.e. purinergic nerves) remains to be established (Richardson & Bouchard, 1975).

The current view is that respiratory reflexes arising from the lungs of mammals can be explained on the basis of three types of vagal endings: the pulmonary stretch receptors, the irritant receptors and the type J receptors (Widdicombe, 1974). The sensory fibres of these receptors run in the vagi and enter the medulla oblongata. The fibres of pulmonary stretch and irritant receptors are myelinated, while type J receptors are supplied by nonmyelinated fibres in the cat, dog and rabbit (Widdicombe, 1974). The properties of these receptors have been based mainly on studies performed in animals. The relevance of these findings in relation to sensory receptor function in human airways is unknown.

Pulmonary stretch receptors are found mainly in the bronchi and smaller airways. It is unclear, however, whether these receptors are located in the bronchial mucosa or smooth muscle (Paintal, 1977). The reflex effects produced by activation of pulmonary stretch receptors are thought to include inhibition of ventilation, relaxation of tracheobronchial smooth muscle, deflation reflex and Head's paradoxical reflex (Paintal, 1977). Irritant receptors were initially described by Knowlton & Larrabee (1946), and are thought to lie between airway epithelial cells (Fillenz & Widdicombe, 1972). Most of these receptors are found in the larynx, the bifurcation of the trachea and at the junction of the larger bronchi (Fillinz & Widdicombe, 1972). The more proximal endings are thought to produce cough, while the main reflex effect from stimulation of those in the intrapulmonary airways are broncho-constriction and hyperpnoea (Widdicombe, 1974). There are species differences in the response of these receptors. In rabbits, excitation is produced by histamine, ammonia vapour and cigarette smoke (Sellick & Widdicombe, 1972), while canine irritant receptors, although sensitive to histamine, are only occasionally excited by ammonia and cigarette smoke (Sampson & Vidruk, 1975). The function of intrapulmonary irritant receptors therefore, remains contraversial, and they are considered by Paintal (1977) to have the same reflex effects as the pulmonary stretch receptors. The third category of receptor has been referred to in various terms, which include type J receptors (Paintal, 1977) and

C-fibre endings in pulmonary and bronchial airways (Coleridge & Coleridge, 1977). The function of this receptor remains speculative and its physiological importance in humans is unknown.

Airway Receptors

In 1948 Ahlquist classified adrenergic receptors into α and β types. β -adrenergic receptors have two distinct subtypes; β_1 receptors are found in heart and adipose tissue and β_2 receptors are found in blood vessels and other types of smooth muscle, in liver and skeletal muscle (Lefkowitz, 1975). Human bronchial smooth muscle contains predominantly β_2 adrenergic receptors, (Fleisch, Kent & Cooper, 1973) and stimulation of these receptors results in broncho-dilation (McFadden, Newton-Howes & Pride, 1970). α -receptors have been reported in the smooth muscle of the airways of guinea pigs, rabbits, cats, old rats and dogs (Castro de la Mata, Penna & Aviado, 1962; Everitt & Cairncross, 1969; Fleisch, Maling & Brodie, 1970; Kneussl & Richardson, 1978). In human tracheal and bronchial smooth muscle, however, α receptors have been demonstrated only in the presence of respiratory diseases such as bronchopneumonia and chronic obstructive airways disease (Kneussl & Richardson, 1978). The α receptor antagonists phenylephrine (Simonsson et al, 1972[a]; Patel & Kerr, 1973), and methoxamine (Snashall, Boother & Sterling, 1978) have been shown to significantly increase airway resistance in asthmatic subjects, while producing either a small effect (Anthracite, Vachon &

Knapp, 1971; Bianco et al, 1972) or no effect (Patel & Kerr, 1973; Snashall et al, 1978) in normal subjects. Cholinergic receptors are found in bronchial smooth muscle of several species (Fillenz, 1970; El-Bermani & Grant, 1975) and anticholinergic drugs result in bronchodilation (Olsen et al, 1965). Ingram et al (1977) and Hensley et al (1978) have suggested that cholinergic antagonists have a greater effect on the more central airways and β agonists have a greater effect on peripheral airways.

H_1 receptors and H_2 receptors are widely distributed throughout the animal body, although the proportion of cells bearing H_1 - and H_2 receptors varies not only with the species, but also with cell source (Chand & Eyre, 1975). In sheep, goats, calves, pigs, horses, guinea pigs and chickens, histamine causes contraction of tracheal and bronchial smooth muscle (Chand & Eyre, 1975). However, Eyre (1973) showed that the relaxant effect of histamine in terminal airway smooth muscles of sheep is mediated via H_2 receptors, and that cat tracheal smooth muscle contains both H_1 and H_2 receptors. It is not clear whether both H_1 and/or H_2 receptors are present in the airways of normal subjects and asthmatic patients, although in vitro experiments suggest that both H_1 and H_2 receptors occur in human bronchial smooth muscle (Dunlop & Smith, 1977).

Specific dopamine receptors have been identified

in renal, mesenteric, coronary and intracerebral arterial vascular beds (Goldberg, 1972; Von Essen, 1972), which when stimulated by dopamine cause vasodilation. It is unknown whether such receptors exist in the human bronchial tree, although recently Key, Cain & Goetter (1978) found specific dopamine receptors in canine bronchial smooth muscle. There may also be receptors on the bronchial smooth muscle for serotonin, bradykinin, angiotensin II, and the prostaglandins. The function of these receptors is unknown, although it has been suggested that they may modulate airways calibre or may serve a purpose in utero or in the neonate (Fleisch et al, 1973).

BRONCHIAL REACTIVITY

General

Patients with asthma have increased airway reactivity to a variety of non-specific stimuli (Orehek et al, 1977[a], which may persist for years in the absence of active asthma (Townley, Ryo & Kang, 1971). This bronchial hyper-reactivity has been demonstrated to histamine (Weiss, Robb & Blumgart, 1929; Curry, 1946), cholinergic drugs (Curry, 1947), bradykinin (Herxheimer & Stresemann, 1961), SRS-A (Herxheimer & Stresemann, 1963), β-adrenergic antagonists (McNeill 1964), prostaglandin $F_{2\alpha}$ (Mathé et al, 1973), dust (Dubois & Dautrebande, 1958), cold air (Wells, Walker & Hickler, 1960), citric acid (Simonsson, Jacobs & Nadel, 1967) and to exercise (McNeill et al, 1966). Some, but not

all, relatives of asthmatics show increased methacholine reactivity, although not to the same degree as seen in symptomatic asthmatics (Townley et al, 1974). Transient bronchial hyper-reactivity has also been demonstrated in normal subjects after spontaneous viral infections (Parker, Bilbo & Reed, 1965; Empey et al, 1976; Little et al, 1978) and after short term exposure to low concentrations of ozone (Golden, Nadel & Boushey, 1978).

Bronchial reactivity is usually reproducible for a given patient (Spector & Farr, 1975), although responses may be influenced by the time of day of testing (DeVries et al, 1962), the overall severity of asthmatic symptoms (Makino, 1966; Muranaka et al, 1974; Cockcroft et al, 1977[a]) and the baseline lung function (Makino, 1966; Benson, 1975; Cockcroft et al, 1977[a]). Recent allergen exposure (Altounyan, 1970) and acute respiratory infections (Parker et al, 1965; Empey et al, 1976) both increase reactivity. $\beta_2$adrenergic agonists, anticholinergic and theophylline drugs may reduce bronchial reactivity (Cockcroft et al, 1977[b]), whereas the effect of corticosteroids on bronchial responses is conflicting (Arkins, Schleuter & Fink, 1968; Spector & Farr, 1975).

The cause of bronchial hyper-reactivity is unknown, although a variety of mechanisms have been proposed:-

(1) Hypertrophy of bronchial smooth muscle

Patients with asthma may have hypertrophy and hyperplasia of bronchial smooth muscle (Dunnill,

Masarella & Anderson, 1969; Houssain, 1973) which could contribute to the increased reactivity of the airway. This mechanism would not account, however, for the decreased threshhold for cough in asthmatics (Bickerman & Barach, 1954) or the increased bronchial reactivity found in normal subjects after viral respiratory tract infections (Parker et al, 1965; Laitinen et al, 1976; Empey et al, 1976) or after exposure to ozone (Golden et al, 1978)

(2) Biochemical abnormalities in bronchial smooth muscle

Szentivanyi (1968) postulated that bronchial hyper-reactivity in asthma resulted from an inherent defect in β adrenergic responsiveness and a relative increase in α adrenergic activity. This hypothesis was based on experiments in normal mice sensitised with an injection of Bordetella pertussis organisms which demonstrated a 30 to 300 fold increased sensitivity to histamine and a 20 to 50 fold increased sensitivity to serotonin. In nonimmunised mice treated with dichloroisoprenaline, a β adrenergic blocking agent, a similar hypersensitivity to the effects of histamine and serotonin developed. In support of this hypothesis, reduced β_2 adrenergic metabolic and cardiovascular responses to sympathomimetic agents or exercise have been found in asthmatic patients (Cookson & Reed, 1963; Middleton & Finke, 1968). Human leukocytes which have β_2 adrenoreceptors (Conolly & Greenacre, 1977), have been reported to show decreased cyclic AMP response to β

stimulants in asthma (Logsdon, Middleton & Coffey, 1972; Parker & Smith, 1973; Alston, Patel & Kerr, 1974; Lee, Bussee & Reed, 1977; Makino et al, 1977). It has been suggested, however, that the diminished β-adrenoceptor response in asthmatic patients may be due to prolonged exposure to large doses of adrenergic bronchodilators (Conolly & Greenacre, 1976; Morris et al, 1978). Further evidence against Szentivanyi's hypothesis is provided by the finding that β-adrenergic blockade with propranolol does not cause asthma in healthy subjects (Zaid & Beall, 1966; MacDonald, Ingram & McNeill, 1967; Richardson & Sterling, 1969). In some, but not all normal subjects, however, the bronchial response to non-specific irritants is increased after β-adrenergic blockade (Zaid & Beall, 1966; MacDonald et al, 1967; Grieco & Pierson, 1971), but this is still less than is seen in asthmatics (Orehek, et al, 1975[a]). Normal subjects, however, develop a progressive loss of airways responsiveness to both inhaled and intravenous salbutamol after regular inhaled salbutamol (Holgate, Baldwin & Tattersfield, 1977) which does not appear to occur in asthmatic patients (Harvey & Tattersfield, 1978).

As well as postulating an inherent defect in β-adrenergic responsiveness in asthma, Szentivanyi (1968) also suggested that there was a relative increase in α-adrenergic activity. α-adrenergic receptors have been found in the airway smooth muscle of the guinea pig, rabbit, cat, rat and dog (Castro de la Mata et al, 1962; Everitt & Cairncross, 1969; Fleisch et al, 1970;

Kneussl & Richardson, 1978). In human tracheal and bronchial smooth muscle obtained at autopsy, α-adrenoreceptors have been demonstrated only in the presence of respiratory diseases such as broncho-pneumonia and chronic obstructive airways disease (Kneussl & Richardson, 1978). A significant increase in airway resistance in asthmatic patients after α-adrenergic stimulation has been reported with the α-adrenoceptor agonists phenylephrine (Simonsson et al, 1972[a]; Patel & Kerr, 1973) and methoxamine (Snashall et al, 1978). In normal subjects, Patel & Kerr (1973) and Snashall et al, (1978) found no airway response to α-adrenoceptor agonists, while small changes were reported by Anthracite et al, (1971) and by Bianco et al, (1972). Recently, vascular and papillary α-adrenergic hyper-responsiveness has been found in asthmatic patients (Henderson et al, 1979).

The α-adrenoceptor antagonist thymoxamine has been reported to prevent histamine, allergen and exercise-induced bronchoconstriction (Bianco et al, 1972; Gaddie et al, 1972; Patel & Kerr, 1975; Patel et al, 1976) but has no effect on methacholine or $PGF_2\alpha$ induced bronchoconstriction (Patel, 1975). The significance of these findings is, however, unclear since thymoxamine, as well as having an α-adrenoceptor antagonist action, also has weak anti-histamine properties and may also stimulate β-adrenergic receptors by virtue of the accumulation of catecholamines from interference with the re-uptake mechanism. The

presence and possible contribution of α -adrenergic hyper-responsiveness to bronchial hyper-reactivity in asthma, therefore, remains to be elucidated.

(3) Increase in resting bronchomotor tone

Benson (1975) has suggested that an increase in the resting state of the airways may contribute to bronchial hyper-reactivity in asthma. Two factors are important in relation to this hypothesis. Firstly, in blood vessels a similar degree of shortening narrows a constricted vessel more than a non-constricted vessel (Folkow, 1956). A similar physical relationship probably holds for airways, so that resistance is inversely related (approximately) to the fourth power of the radius. Experiments on dogs, in which changes in bronchial calibre were measured with tantalum bronchograms and compared with measurements of airways resistance, have shown that if there is pre-existing airway narrowing then a small reduction in calibre produces a large increase in resistance (Benson & Graf, 1977). Secondly, resting bronchomotor tone may be important. Thus, drugs relaxing airway smooth muscle may produce a tissue unresponsive to constrictor influences.

In support of this hypothesis an inverse correlation between baseline lung function and reactivity has been found by several workers (Makino, 1966; Cockcroft et al, 1977[a]). Brown, McFadden & Ingram (1977) found that inhaled histamine produced similar changes in residual

volume, vital capacity and total lung capacity between a small group of atopic and non-atopic subjects whose baseline lung function was normal. Several other studies, however, have found no relationship between bronchial reactivity to methacholine, histamine or allergen and airways calibre in patients whose baseline lung function was either normal, abnormal or affected by inhaled bronchodilator drugs. (Cade & Pain, 1971; Bryant & Burns, 1976[b]; Fish et al, 1976; Cockcroft et al, 1977[b]; Rubinfield & Pain, 1977; Cockcroft, Ruffin & Hargreave, 1978; Mellis et al, 1978).

(4) Increased mast cell sensitivity

Bronchial lumen mast cells from rhesus monkeys with airway reactivity to ascaris antigen will transfer this reactivity to recipient animals (Patterson et al, 1978). These authors have proposed, therefore, that bronchial lumen mast cells may be the major effector cell in non-specific bronchial reactivity. In support of this hypothesis mediator release has been produced by non-immunological mechanisms in sensitized guinea pig and human lung specimens (Vane, 1971; Seale & Piper, 1978). Monkeys sensitized with passively transferred allergic serum, however, although showing responses to specific allergen (Paterson et al, 1965; Radermecker, Guebelle & Salmon, 1972), show no increase in non-specific reactivity to histamine (Radermecker et al, 1972).

In humans, some studies have reported finding no correlation between bronchial hyper-reactivity and serum

level of total IgE, or the number of allergens giving positive prick test reactions (Cade & Pain, 1971; Muranaka et al, 1974; Bryant & Burns, 1976(b); Woolcock, Colman & Jones, 1978), although Cockcroft et al, (1977(a)) found a direct association between atopic status and the level of reactivity. Furthermore, as pointed out by Bryant & Burns (1976(a)), there may still be an association between bronchial reactivity and the amount of IgE fixed to the bronchi, because the amount of cell fixed IgE bears no correlation to the serum level of IgE (Ishizaka, Soto & Ishizaka, 1973). This mechanism would not account, however, for the decreased threshhold for cough in asthmatics (Bickerman & Barach, 1954) or the increased bronchial reactivity found in normal subjects after viral respiratory tract infections (Parker et al, 1965; Laitinen et al, 1976; Empey et al, 1976).

(5) Increased sensitivity of irritant receptors

Nadel (1973) has suggested that sensitization of vagal irritant receptors in the airway epithelium may play an important role in causing bronchial hyper-reactivity. The evidence for this hypothesis has been based mainly on studies in experimental animals. Mechanical and chemical stimulation of the airways in animals produces bronchoconstriction which can be prevented by vagotomy (Nadel, 1973), thus implicating cholinergic vagal pathways in these responses. The chemical mediator histamine constricts airway smooth muscle by direct

local effect (Dale & Laidlaw, 1910), and also causes bronchoconstriction which is reduced by vagotomy or by atropine (DeKock et al, 1966; Mills & Widdicombe, 1970; Gold, Kessler & Yu, 1972). The same aerosol stimulates lung irritant receptors which are known to cause reflex bronchoconstriction (Mills, Sellick & Widdicombe, 1969; Vidruk et al, 1977). The relative strength, however, of direct and reflex actions of histamine on the airways is controversial. The findings in some studies have suggested that the vagus nerve plays both a relatively minor (Loring, Drazen & Ingram 1977; Loring et al, 1978; Hahn et al, 1978), and major (Gold et al, 1972) role in the pulmonary response to aerosol histamine. The discrepancy between these studies may be due to differences in methodology (Hahn et al, 1978; Jackson & Richards, 1977). Loring et al, (1978) and Benson & Graf (1977), however, suggested that vagal efferent actively may modulate histamine response by producing a higher constant level of smooth muscle activation or baseline tone.

In several animal species allergen induced bronchoconstriction is reduced by vagotomy or by atropine (Mills & Widdicombe, 1970; Gold et al, 1972), and in rabbits allergen has been shown to stimulate lung irritant receptors resulting in reflex broncho-constriction (Mills et al, 1969). In experiments reported by Gold et al, (1972) allergen induced bronchoconstriction in dogs sensitive to Ascaris suis could be prevented by differential afferent and efferent

vagal blockade. Application of allergen to one lung caused bronchoconstriction in the opposite lung, which could be abolished by afferent vagal blockade of the lung receiving the allergen. These results suggest, therefore,that the parasympathetic nervous system may play an important role in the airway response to antigen, chemical mediators and non-specific stimuli in experimental animals.

Evidence in support of the hypothesis that reflex bronchoconstriction may be an important component of the airway changes in human asthma has been based on a number of factors:-

(a) The analogy between the bronchomotor mechanisms analysed in the experimental animal and the overall responses in man suggests that the same reflexes are involved (Widdicombe, 1975). There are, however, some striking differences between species. Guinea pigs have different structured airways than man and the reaginic antibody is IgG and not IgE. Experimental asthma produced in dogs and monkeys is of an acute and not a chronic form. The Hering-Breur reflex is strong in dogs and cats but weak in man (Widdicombe, 1961). Thus only tentative conclusions should be drawn between animal experiments and human asthma.

(b) Surgical denervation of the lungs in asthma The results have been generally poorly documented although Dimitrov-Szokodi, Husvéti & Balogh (1957) reported that surgical pulmonary denervation produced clinical

improvement and decreased bronchial responses to histamine. However, the lack of any long term improvement in most studies is not surprising since denervation can produce hyper-reactivity (Gold, 1975). In addition, after experimental lung implantation both efferent and afferent vagus pathways may regenerate (Edmunds, Graf & Nadel, 1971).

(c) Afferent vagal nerve blockade in asthma Local anaesthetics have been used to inhibit afferent vagal sensory endings in animals (Jain et al, 1973; Dain, Boushey & Gold, 1975). In patients with asthma, Petit & Dalhez (1970) studied the effect of inhaled lignocaine combined with ephedrine, although inclusion of ephedrine makes interpretation of their results difficult. More recently, Cross et al, (1976) demonstrated that an aerosol of bupivacaine hydrochloride can produce reversible anaesthesia of the airways in man, which inhibited the cough reflex, and abolished the afferent pathway of a reflex induced bronchoconstriction in one normal subject. Using a canine model of reflex bronchoconstriction, Jackson & Richards (1977) suggested that sodium cromoglycate may reduce the activity of lung irritant receptors, and by this means decrease asthmatic attacks in man.

(d) Bronchial hyper-reactivity in human subjects Nadel, (1977) has suggested that the decrease in threshhold of irritant receptors in the airways could explain the

increased cough response to inhaled stimuli that exists in asthmatics (Bickerman & Barach, 1954). Viral respiratory tract infections cause transient damage to the airway epithelium (Hers & Mulder, 1961) and this may be a possible mechanism causing sensitization of irritant receptors (Nadel, 1977). Healthy human subjects with spontaneous viral infections (Empey et al, 1976) or with innoculations of live attenuated influenza virus (Laitinen et al, 1976) show exaggerated cough responses and histamine responses which are prevented and reversed by atropine sulphate. Similar hyper-reactivity to methacholine has also been reported (Parker et al, 1965; Little et al, 1978). Furthermore, ozone which causes desquamation and degeneration of bronchial epithelial cells (Boatmann, Sato & Frank, 1974) produces bronchial hyper-reactivity to histamine which is prevented by atropine sulphate (Golden et al, 1978).

(e) The effect of anticholinergic drugs There is controversy over the clinical effectiveness of cholinergic blocking agents in asthma. Gold (1975) has suggested that the dose of atropine required to block antigen induced bronchoconstriction in humans is large (3 mg IV or 40 mg by aerosol), exceeding the dose needed to block normal airway tone. In animals 0.5-2.0 mg/Kg is required to block bronchoconstriction induced by electrical stimulation of the vagus (Widdicombe & Sterling, 1970). In addition, anticholinergic drugs relax bronchial smooth muscle

which may alter its responsiveness to constrictor influences. These points must, therefore, be considered in the analysis of any experiments involving anticholinergic drugs.

Cholinergic blocking drugs have been reported to reduce the bronchoconstrictive effect of a number of nonantigenic stimuli in asthmatic patients including methacholine (Altounyan, 1964; Grieco & Pierson, 1970; Itkin & Anand, 1970), citric acid (Simonsson et al, 1967), β-adrenergic antagonists (Grieco & Pierson, 1971), dusts (Simonsson et al, 1967), bradykinin (Simonsson et al, 1973) and cold air Simonsson et al, 1967). Atropine sulphate at doses up to 1.2 mg and ipratropium bromide at doses up to 1 mg have been reported to prevent $PGF_{2\alpha}$ induced bronchoconstriction (Atlanko & Poppius, 1975; Patel, 1975; Mathé & Hedquist, 1975; Orehek et al, 1977[b] although Newball & Lenfant (1977) found no reduction in the effects of very large doses of $PGF_{2\alpha}$ with atropine. Inhaled atropine sulphate (dose range 290 µg to 5 mg) and ipratropium bromide (dose range 40 µg to 80 ug) have been found in most studies in asthmatic patients to cause a slight but significant reduction in the bronchoconstriction produced by inhaled histamine (Altounyan, 1964; Simonsson et al, 1967; Harnett & Spector, 1976; Casterline, Evans & Ward, 1976; Cockcroft et al, 1977[b]) although this has not been found by other workers (Itkin & Anand, 1970; Woenne et al, 1978). The main site of action of histamine on the airways of asthmatic

patients is, therefore, probably not via cholinergic pathways (Casterline et al, 1976).

The effect of anticholinergic drugs on antigen induced early asthmatic responses has been found to vary within and between different studies. In studies using a single antigen dose, inhaled and intravenous atropine sulphate and inhaled ipratropium bromide were effective in protecting against early asthmatic responses in eight out of 20 patients (Itkin & Anand, 1970), five out of seven patients (Yu, Galant & Gold, 1972), seven out of 10 patients (Orehek & Gayrard, 1977) and five out of 10 patients (Ruffin, Cockcroft & Hargreave, 1978). Cockcroft et al, (1978) found that ipratropium bromide (dose 80 µg) produced a slight and variable reduction in the early asthmatic responses in 12 asthmatic patients. In studies using antigen dose-response curves Fish et al, (1977) and Rosenthal et al, (1977) found anticholinergic drugs to be ineffective. These workers suggested, however, that there may possibly be a cholinergic effect of antigen at low doses. The reason for the apparent variation in effectiveness of inhaled anticholinergic drugs in preventing antigen induced asthma between different asthmatics is unexplained, but may be due to different techniques of antigen challenge, dose of cholinergic antagonists and unidentified differences between asthmatic patients (e.g. main site of airflow obstruction).

The relative importance of the parasympathetic

nervous system in the airway response to antigen, chemical mediators and non-specific stimuli in humans has therefore not been fully resolved.

EXERCISE-INDUCED ASTHMA

For over 250 years exercise-induced asthma (EIA) has been recognised to occur in asthmatic patients (Floyer, 1717). Jones, Buston & Wharton (1962) demonstrated that exercise for 1-2 min duration is often followed by a decrease in airflow obstruction, but if exercise is prolonged for up to 8 min increased airflow obstruction, usually maximal at 5 min after completion of exercise, may occur. The incidence of clinically significant EIA in adult asthmatics is probably about 50% (Turner-Warwick, 1978), rising to over 70% in children (Silverman & Anderson, 1972).

Several factors influence the response of asthmatic patients to exercise. Running has been reported to be a more potent stimulus for inducing EIA than cycling, while swimming and walking were found to have very little effect (Godfrey, Silverman & Anderson, 1973). The specificity of exercise, however, as a provocative factor for asthma probably depends on the relationship of physical work load to exercising muscle mass and the effect this has on minute ventilation (Strauss et al, 1977[a]; McFadden & Ingram, 1979). There is also a direct relationship between pre-existing airway obstruction and the magnitude of response post-exercise (Haynes, Ingram & McFadden, 1976; Schachter et al, 1978).

Recently the temperature and humidity of inspired air has also been shown to alter the response to exercise. Thus an increase in severity of EIA occurs with cold air breathing (Strauss et al, 1977[b]; Deal et al, 1978) and dry air breathing (Strauss et al, 1978). If the methods used to evaluate EIA are standardized then there is good reproductibility between study days, and within the same day provided the exercises are performed at least 2-4 hours apart (Eggleston & Guerrant, 1976; Haynes et al, 1976; Edmunds, Tooley & Godfrey, 1978). The variation of a subject's response is reduced by selecting only those subjects with greater than 20% change in FEV_1 and by completing studies over a short period of time (Eggleston & Guerrant, 1976; Haynes et al, 1976).

Pathogenesis

Several mechanisms have been postulated to explain the pathogenesis of EIA:-

(1) Hyperventilation has been suggested to be an important factor in EIA by several workers (Crompton, 1968; Chan-Yeung, Vyas & Grzybowski, 1971)although this was not confirmed by others (Silverman, Anderson & Walker, 1972; Allen et al, 1973; McFadden et al, 1977[a]). More recently, however, it has become clear that the sustained high minute ventilation during exercise, and the effect this has on inspired air temperature and humidity, is an important initiating factor in EIA (Zeballos et al, 1978; McFadden &

Ingram, 1979).

(2) Hypocapnia as a result of hyperventilation has been postulated to produce airways narrowing (Herxheimer, 1946; Fisher et al, 1970). Fisher & Hansen (1976) found that the inhalation of carbon dioxide relieved EIA by an action on large and small airways. Other studies have failed to find any relationship between carbon dioxide levels and EIA (Silverman et al, 1972; Allen et al, 1973; McFadden et al, 1977[a]). Carbon dioxide may, however, exert a modulating influence in EIA by either reducing airflow obstruction or enhancing the effects of other bronchoconstrictive stimuli (McFadden et al, 1977[a]).

(3) Metabolic acidosis due to hydrogen ions or lactic acid has been thought to induce asthma after exercise (Vassallo, Gee & Domm, 1972). Elevated arterial hydrogen ion and/or lactic acid concentrations have been found after exercise in asthmatic patients (Fisher et al, 1970; Vassallo et al, 1972; Strauss et al, 1977[c]) and these could possibly cause formation and release of mediators of immediate hypersensitivity. Treatment, however, with sodium bicarbonate or sodium lactate sufficient to correct the metabolic acidosis fails to prevent EIA (Seaton et al, 1969; Strauss et al, 1977[c]). Furthermore, the degree of lacticacidaemia does not correlate with the severity of EIA (Silverman et al, 1972; Katz et al, 1971).

(4) β adrenergic blockade It has been suggested that the imbalance of the autonomic system in asthma postulated by Szentivanyi (1968) may be central to the pathogenesis of EIA. In some studies the α -receptor antagonists phentolamine, indoramin and thymoxamine (Gross, Souhrada & Farr, 1974; Bianco et al, 1974; Patel et al, 1976) were reported to prevent EIA, whereas Sly et al, (1967) were unable to inhibit EIA in 10 asthmatics with IV pentolamine. Unfortunately, none of these agents is specific for the α -receptor; phentolamine increases circulating catecholamine concentrations (Nikerson & Collier, 1970) and directly inhibits smooth muscle action (Taylor et al, 1965), indoramin and thymoxamine have H_1 receptor antagonist actions (Birmingham & Szolcsányi, 1965; Alps et al, 1972).

(5) Type I mediator release Several authors have suggested that exercise provokes type I mediator release from mast cells (Godfrey, 1975). This hypothesis is based on the finding that sodium cromoglycate, which inhibits the release of type I mediators from mast cells (Orr et al, 1970), may prevent EIA through a similar mechanism (Davies, 1968; Godfrey & König, 1976; McFadden et al, 1977[b]). Exercise may cause mediator release from sensitized mast cells through a non-immunological mechanism (Vane, 1971; Seale & Piper, 1978). Neither EIA, however, nor the protective effect of sodium

cromoglycate correlate with total serum IgE levels (Fitch, Turner & Morton, 1972; Morton, Turner & Fitch, 1973), although serum concentrations of IgE may not correlate with cell fixed antibody (Ishizaka et al, 1973).

The primary type I mediators released from mast cells in vitro are histamine, SRS-A, ECF-A, and PAF; bradykinin and prostaglandin are considered secondary mediators (Austen & Orange, 1975). It has been suggested that β agonists may have both bronchodilator and mast cell membrane stabilizing actions (Anderson et al, 1976; Hetzel, Batten & Clark, 1977; Gibson et al, 1978; Ferris et al, 1978). Increased arterial plasma histamine levels have been found after exercise in asthmatics (Ferris, Anderson & Temple, 1978), and the effect of H_1 receptor antagonists in EIA has been examined in a few patients. No significant protective action was found with parenteral mepyramine maleate (50 mg) in 5 asthmatics (McNeill et al, 1966) or in 2 asthmatics with oral chlorpheniramine (4 mg) Bianco et al, 1974). Diethylcarbamazine has been shown to inhibit release of SRS-A in the rat (Orange, Valentine & Austen, 1968) and SRS-A and histamine from passively sensitized monkey lung tissue following antigenic challenge (Ishizaka et al, 1971). Sly & Matzen (1974) found that inhaled diethylcarbamazine protected against EIA in 15 out of 20 asthmatic children, and suggested that this supported the postulate that mediator release was an important mechanism in EIA.

Corticosteroids in a single dose, either parenterally or by inhalation, just prior to exercise does not significantly prevent EIA (McNeill et al, 1966; König, Jaffe & Godfrey, 1974) whereas prolonged inhaled betamethasone valerate may reduce EIA (Hodgson, McPherson, Friedman, 1974; Hartley, Charles & Seaton, 1977). Hartley et al, (1977) postulated that prolonged steroids may be acting by interfering with the synthesis or release of mediators from mast cells. The prostaglandin synthetase inhibitors aspirin and indomethacin have no effect on EIA (Smith & Dunlop, 1975; Rudolf et al, 1975).

(6) Reflex vagal bronchoconstriction In experimental animals it has been postulated that allergen-induced bronchoconstriction is due to stimulation of irritant receptors in the bronchial epithelium, which elicit reflex vagal bronchoconstriction (Gold, 1975; Widdicombe, 1977). A similar mechanism may occur in human asthma, including EIA. Circumstantial evidence for reflex bronchoconstriction in EIA is based on blocking efferent motor actions with anticholinergic drugs. The protective action of cholinergic blocking agents is, however, variable (Table I). The dose of atropine sulphate required in animals to block bronchoconstriction induced by stimulation of the vagi is between 0.5 mg/Kg to 2.0 mg/Kg body weight, which is higher than could be safely given to humans (Widdicombe & Stirling, 1970). Tinkelman, Cavenaugh & Cooper

TABLE I Effect of anticholinergic drugs in prevention of exercise-induced asthma in different studies

Study	Design of Study	Pulmonary function measurement	Drug	Dose	Method of administration	Effect of E.I.A.
Jones et al., (1963)	S.B.	FEV_1	Atropine	0.01-0.03mg/Kg	S.C.	B/2/6*
McNeill et al., (1966)	S.B.	FEV_1	Atropine	0.6-1.2 mg	S.C.	B/0/5
Sly et al., (1967)	S.B.	PEF	Atropine	0.01 mg/Kg	I.V.	B/4/10
Crompton (1968)	S.B.	FEV_1	Atropine	0.6 mg	S.C.	B/0/1
Fisher et al., (1970)	S.B.	Raw	Atropine	1.6-2.0 mg	I.V.	B/0/2
Simonsson et al., (1972) (b)	S.B.	Gaw	Atropine	1.0-1.5 mg	I.V. & inhaled	B/6/9
Poppius et al., (1972)	D.B.	PEF	Ipratropium	80 ug	Inhaled	No significant protection (N=22)
Stemmann et al., (1975)	S.B.	FEV_1	Ipratropium	40 ug	Inhaled	Significant protection (N=20)
Fisher & Hansen (1976)	S.B.	Raw	Atropine	1.2 mg	I.V.	B/0/4
Tinkelman et al., (1976)	S.B.	FEV_1	Atropine	0.1 mg/Kg	Inhaled	B/13/18
Godfrey & König (1976)	S.B.	PEF	Atropine	2.0 mg	Inhaled	B/3/7
Chan-Yeung (1977)	S.B.	FEV_1	Ipratropium	80 ug	Inhaled	B/8/9
McFadden et al., (1977) (b)	S.B.	FEV_1	Ipratropium	?	Inhaled	B/5/12
Borut et al., (1977)	D.B.	FEV_1	Atropine	1 mg	Inhaled	No significant protection (N=20)
Borut et al., (1977)	D.B.	FEV_1	Ipratropium	80 ug	Inhaled	No significant protection (N=20)
Deal et al., (1978)	S.B.	FEV_1	Atropine	4 mg	Inhaled	B/3/9

*B/2/6 = blocked EIA in 2 out of 6 patients

S.B. = single blind ; D.B. = double blind ; S.C. = subcutaneous : I.V. = intravenous

(1976) suggested that the lack of inhibition in some studies may be due to insufficient cholinergic blockade. The interpretation of studies using anticholinergic drugs is also complicated because these agents relax bronchial smooth muscle tone, which may alter its responsiveness to constrictor influences (Benson, 1975).

Recently McFadden & Ingram (1979) have suggested that airway cooling is the primary stimulus in EIA, and that this depends on the level of minute ventilation, inspirated air temperature and water content. An increase in severity of EIA occurs with cold (Strauss et al, 1977[b]; Deal et al, 1978) and dry air breathing (Strauss, et al, 1978). When the inspired air is adjusted to 38^{o}C and 100% humidity then EIA is inhibited (Chen, Horton & Souhrada, 1976; Strauss et al, 1978). The mechanism by which cold, dry air potentiates EIA is unknown. Nasal breathing during exercise (Shturman-Ellstein et al, 1978) and local anaesthesia of the oropharynx (McNally, Enright & Souhrada, 1978) have both been reported to almost completely prevent EIA. These authors suggested that EIA is mediated through stimulation of irritant receptors located in the oropharynx by relatively cool, dry air when mouth breathing is used. The local anaesthetic lignocaine, however, as well as possibly blocking irritant receptors also has an inhibitory effect on mast cell release of mediators (Weiss, Hargraves & Viswanath, 1978). Furthermore, sodium

cromoglycate has been found to have a protective effect on cold induced bronchospasm (Breslin & Pepys, 1975). Dean et al, (1978) found that vagal efferent blockade does not prevent the potentiation of EIA produced by breathing cold air. They suggested that mast cells within the surface of the mucosa could be directly stimulated to release mediators of immediate hypersensitivity by alteration in the temperature of the environment as occurs in cold urticaria (Wasserman et al, 1977).

The mechanism of EIA may be multifactorial. In an uncontrolled study reported by McFadden et al, (1977[b]) the combination of sodium cromoglycate and the anticholinergic drug ipratropium bromide inhibited EIA in all patients studied, whereas ipratropium bromide alone inhibited only those patients with mainly large airways obstruction as assessed by changes in density dependence of maximal expiratory flow rates. Sodium cromoglycate was not given alone. They concluded that the airway response to exercise in asthmatics is heterogeneous in terms of predominant site of flow limitation and this factor appears to relate to mechanisms i.e. reflex vagal bronchoconstriction and direct airway narrowing secondary to the release of type I mediators from mast cells.

AIM OF THE STUDY

In allergic patients, acute bronchoconstriction to inhaled allergens is thought to be due to the

liberation of chemical mediators from mast cells. Mediators such as histamine, slow-reacting substance of anaphylaxis, and in some species dopamine, have a direct local effect upon the airways. In addition, recent evidence in animals and man suggests that antigen-induced bronchospasm may also occur through activation of irritant receptors in the bronchial epithelium, which elicit reflex vagal bronchoconstriction (Gold, 1975; Widdicombe, 1977). Non-specific irritants may also cause bronchospasm in susceptible individuals by stimulation of irritant receptors. Similarly, it has been postulated that exercise-induced asthma may be due to the release of chemical mediators from mast cells (Godfrey, 1975), and that these mediators may act either directly upon bronchial smooth muscle or via reflex vagal pathways (Figure I). The aim of this study was, therefore, to define the relative importance of the direct and reflex vagal effects of chemical mediators, non-specific stimuli and exercise upon the airways of normal subjects and patients with asthma.

Firstly, the possible sites of action of chemical mediators upon bronchial smooth muscle were examined. Histamine is thought to be an important primary mediator released from human mast cells (Austen & Orange, 1975), while, in some species dopamine has been implicated in type I hypersensitivity (Eyre & Deline, 1971). Two types of histamine receptor (Ash & Schild, 1966; Black et al, 1972) and specific dopamine receptor (Goldberg, 1972; Von Essen, 1972) have been identified in human

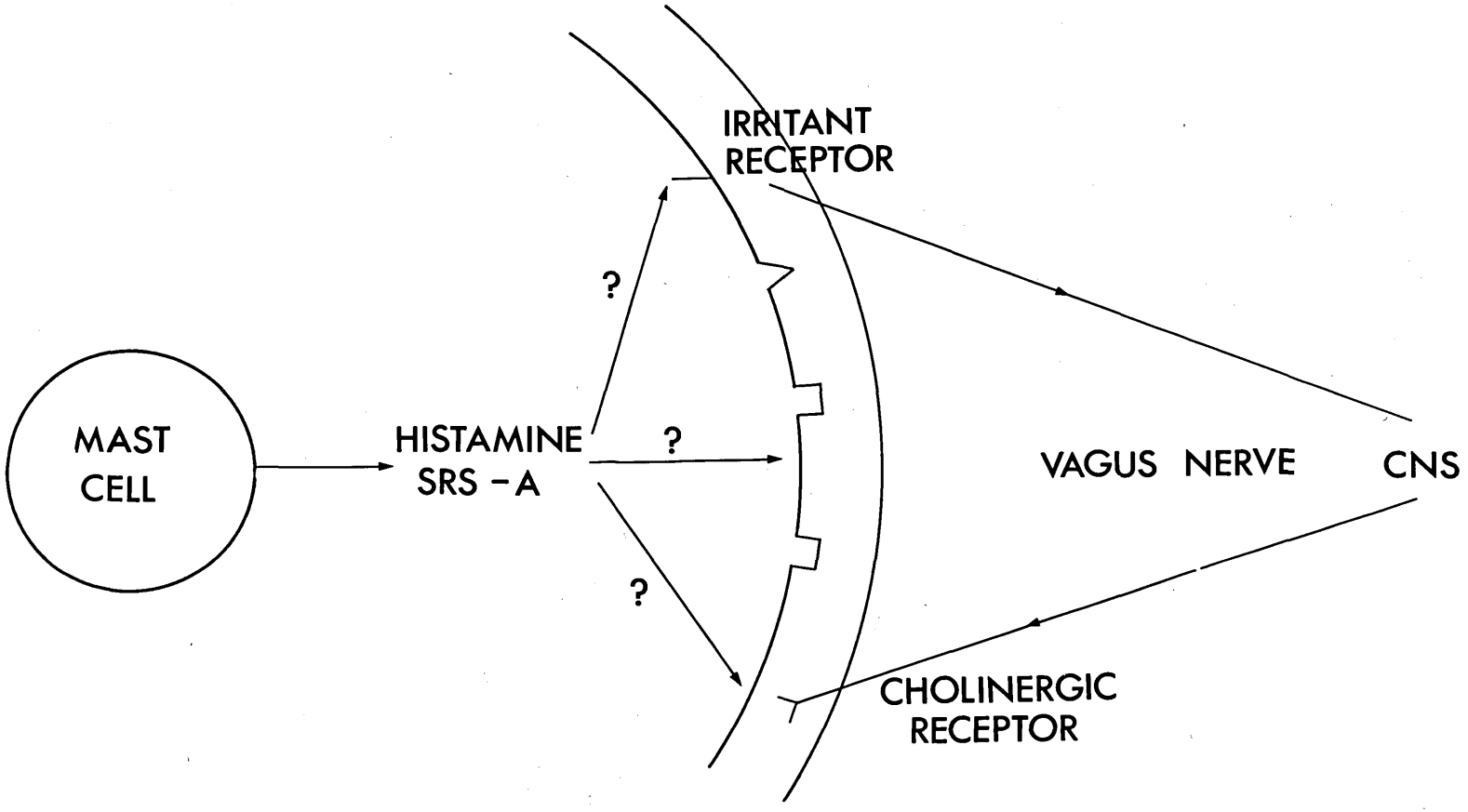

FIGURE I SCHEMATIC REPRESENTATION OF THE AIRWAYS

tissue, and recent *in vitro* studies have suggested that H_1 and H_2 receptors and specific dopamine receptors are present in human and canine bronchial smooth muscle respectively (Dunlop & Smith, 1977; Key, Cain & Goetter, 1978). The bronchial response to histamine and dopamine was studied in normal subjects and asthmatic patients to determine whether H_1 receptor, H_2 receptor and dopamine receptor responses were present in the airways.

The effects of afferent and efferent vagal blockade on experimental bronchoconstriction in normal subjects and asthmatics were then examined. Circumstantial evidence for reflex vagal bronchoconstriction in humans is based on blocking efferent vagal motor action by anticholinergic drugs (Yu *et al*, 1972; Empey *et al*, 1976). In an attempt to develop a more direct method of studying reflex vagal pathways, the effect of an anaesthetic aerosol of bupivacaine in blocking afferent vagal endings was studied.

The pathogenesis of exercise-induced asthma is unknown, but both the release of chemical mediators from mast cells (Godfrey, 1975) and reflex vagal bronchoconstriction secondary to stimulation of irritant receptors (Gold, 1975) have been postulated. Exercise-induced asthma is a safe and reproducable experimental model of acute asthma, and was, therefore, ideally suited for this study. It was hoped that the information obtained from the earlier parts of the

thesis could be applied to this experimental model. The role of chemical mediators in exercise-induced asthma could, therefore, be examined using drugs which prevent mediator release from mast cells, and agents which block the effect of type I mediators on the airways, while vagal pathways could be studied by blocking afferent and efferent vagal endings.

CHAPTER II

MATERIALS AND METHODS

HUMAN VOLUNTEERS

Normal Subjects

Fourteen male and eight female normal subjects (aged 22-37 years ; mean $\pm$ ISD 26.5 $\pm$ 4.6) with no history of chronic respiratory disease and no personal or family history of asthma or other atopic condition were studied. Nine subjects smoked 10 - 15 cigarettes per day.

Asthmatic Patients

Twenty six male and 32 female patients (aged 17-45 years ; mean $\pm$ ISD 24.7 $\pm$ 6.6) with extrinsic asthma and reversible airflow obstruction were studied. All had positive skin tests to at least one inhalant allergen and total serum IgE concentration about 200 U/ml. Sodium cromoglycate and bronchodilators were discontinued for 12 - 24 h before each test. Patients on oral or aerosol corticosteroids were excluded from the study, as were patients who gave a history of a recent respiratory infection. All patients were non-smokers. Baseline data on individual patients is tabulated separately for each study.

The nature and the purpose of each study were explained to both patients and normal subjects. In those patients who were below 18 years of age informed consent was obtained from their parents. All investigations were approved by the Ethical Committee of this hospital and all patients and normal subjects gave informed consent.

METHODS

Body Plethysmography

The constant-volume plethysmograph (DuBois et al, 1956(b); DuBois, Botelho & Comroe, 1956(b)) used in this study was manufactured by Fenyves & Gut (Basle, Switzerland). The chamber was fitted with a large window in the front wall, and a Perspex door with an electro-magnetic catch (Figure 2). A calibration pump for the chamber was incorporated. The volume of the plethysmograph was 690 litres. A heated air selector allowed the subject to be connected either to the outside air, the chamber or the BTPS breathing bag. Pressure changes in the plethysmograph were monitored by a capacitive differential pressure transducer (Fenyves & Gut, Basle) (sensitivity 0.001 - 0.2 kPa : frequency response linear 50Hz) backed off against a rigid metal container (volume 50 litres) to stabilize against thermal drift. Pressure changes at the mouth produced by the inspiratory effort against the closed shutter were measured by a differential pressure transducer (Fenyves & Gut, Basle) (sensitivity 0.5 - 5 kPa : frequency response flat to 50Hz) backed off against the interior of the box. Airflow was measured with a heated Fleisch pneumotachograph and differential pressure transducer (Fenyves & Gut, Basle) with a linear response to 14 l/sec (frequency response flat to 50Hz). Box and mouth pressure plus airflow were plotted on an X-Y recorder (Hewlett Packard, 7041A) with a writing speed of more than 75 cm/sec and a linearity better than 0.2% Box Pressure, mouth pressure and flow were calibrated before each experiment.

FIGURE 2 CONSTANT-VOLUME PLETHYSMOGRAPH

The subject sat in the closed body plethysmograph and as the temperature of the air rose, a pressure compensation switch was periodically turned off until there was no further pressure drift. The subject then applied a nasal clip and panted shallowly through the pneumotachograph at approximately two cycles per second and at a flow rate of 0.5 l/sec. Panting was carried out with open glottis and with checks supported by the hands. On the first visit the technique of panting was demonstrated and the subject practiced breathing against the closed shutter until satisfactory recordings were obtained. While the subject panted the pressure compensation switch was turned off and changes in box pressure and airflow recorded on the X-Y recorder, followed by changes in box pressure and mouth pressure while the subject panted against the closed shutter, which was automatically closed at end-expiration. This was then repeated on a further four to six occasions, the subject resting between each pair of recordings of airway resistance (Raw) and end-expiratory thoracic gas volume (Vtg). Thus Raw and Vtg were measured simultaneously at or near functional residual capacity (FRC). All plethysmographic measurements were carried out by myself, but analysis of the records of pressure and flow was carried out by another person (R.J.) who was unaware of the nature or order of agents administered. The results were expressed as specific conductance (sGaw), which is the reciprocal of airways resistance per litre of thoracic gas volume. The mean of four or six readings was taken as sGaw.

Vtg was calculated using the following formula:

$$Vtg\ (ml) = K_{Vtg}\ \frac{a}{b}\ (B-47) - V_{Korr}$$

Where K_{Vtg} was a standardisation factor for Vtg dependent on range taken for box and mouth pressures, a and b (Figure 3), B was barometric pressure and V_{Korr} was composed of the following values; apparatus deep space: 140 ml, stomach volume with good diaphragm breathing: 170 ml (Bedell et al, 1956).

Raw was calculated using the following formula:

$$Raw = K_{Raw}\ \frac{(B - 47)}{Vtg}\ \frac{c}{d} - 0.25$$

Where K_{Raw} was a standardisation factor for Raw dependent on range taken for flow and box pressure, B was barometric pressure, c and d (Figure 3), and the constant 0.25 takes into consideration the resistance of the mechanical equipment between mouthpiece and breathing bag.

Spirometry

Spirometric recordings were measured either on a water-sealed spirometer (Pulmotest Godart, Holland) or a dry wedge spirometer (Vitalograph, Buckingham, England). The water-sealed and dry wedge spirometer were calibrated prior to each study. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured in triplicate with the subject always seated.

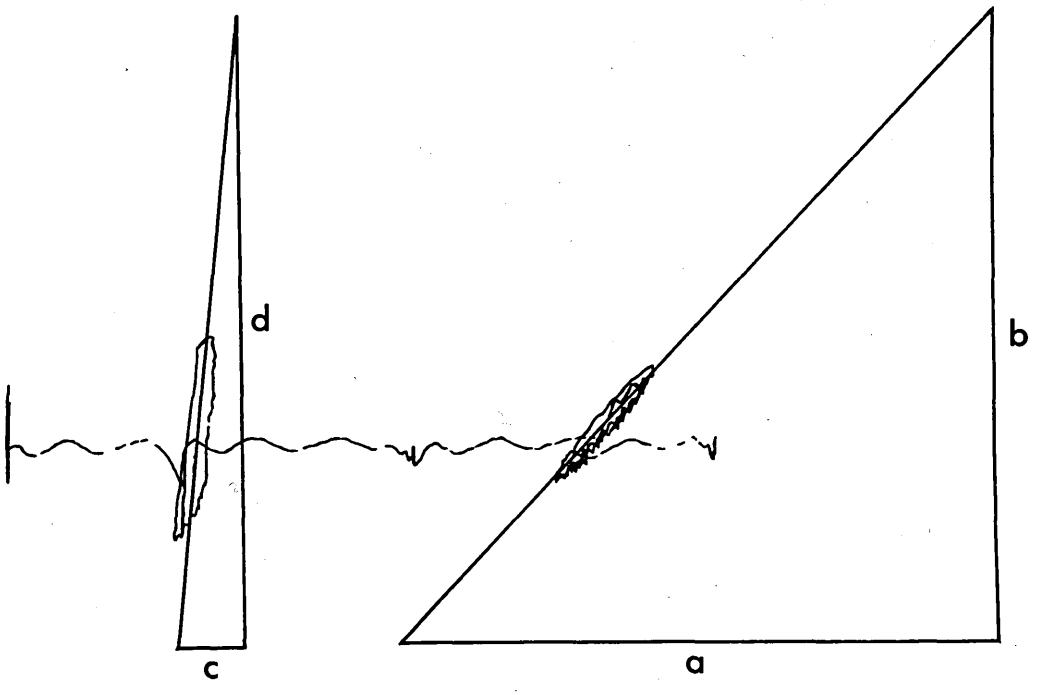

FIGURE 3 CURVES USED TO CALCULATE Raw AND V_{tg}

(Normal subject R.J. 30 min following ipratropium bromide)

The forced expiratory manoeuvre was explained to each subject prior to recording, and only those subjects in whom consistant readings were obtained were included in any of the studies. Spirometric recordings always followed the measurement of sGaw to avoid reflex changes in airways resistance (Orehek et al, 1975[b]). Maximum mid-expiratory flow rate (MMEF), which is the average flow rate over the middle half of the forced expiratory spirogram (Godart spirometer only) was also calculated. The best recording in each case was used for analysis. Volumes were corrected to body temperature, pressure saturated with water vapour (BTPS). Predicted normal values were taken from Cotes (1975) and from Cherniak & Raber (1972) for MMEF.

Flow Volume Curves

Similar instructions to the subject and precautions were used in measurement of maximal expiratory flow volume (MEFV) curves as have been described for the measurement of FEV_1 and FVC. The MEFV curves breathing air were produced using a heated Fleisch pneumotachograph and differential pressure transducer (Fenyves & Gut, Basle) with a linear response to 14 l/sec (frequency response flat to 5OH3) and recorded on a direct writing X-Y recorder (Hewlett Packard 7041A with a writing speed of more than 75 cm/sec and a linearity better than 0.2%) during forced expiration from total lung capacity (TLC) to residual volume (RV). No distortion of the MEFV curve for expiratory flows at 50% vital capacity occurred

from the direct use of an X-Y recorder (Pollock et al, 1977). The MEFV curves were measured in triplicate with the subject seated.

After these recordings were completed, the subject breathed a gas mixture of 79% helium He and 21% O_2 (He-O_2) for at least one minute, which included three deep inspirations. The MEFV curves were measured again, and this was repeated on at least three occasions. The curves with the highest maximal flows whose vital capacities (VC) on air and HE-O_2 matched were used for analysis. The expiratory flows at 50% VC breathing air ($\dot{V}_{50AIR}$) and He-O_2 ($\dot{V}_{50He}$) were measured, and the degree of density dependence was assessed as the ratio of $\dot{V}_{50He}$ to $\dot{V}_{50AIR}$. Responders were those subjects in whom the ratio $\dot{V}_{50He}$ to $\dot{V}_{50AIR}$ was over 1.20. Volumes were corrected to BTPS. The pneumotachograph was calibrated for air and He-O_2 prior to each study with a one litre pump.

Nebulisation

The inhalation of drugs was by means of a Wright nebuliser (Aeorsol Products (Colchester) Limited, London) using compressed air at a flow rate of 8 l/min by means of a portable air compressor (CFIB Aerolyser Electric Inhaler; Aerosol Products (Colchester) Limited, London). Throughout the experiments a separate nebuliser was used for each drug in order to prevent any drug contamination. Nebulisers were cleaned with "Concentrate RBS25" (Chemical Concentrates (RBBS) Limited,

London). Each nebuliser had a capacity of approximately 15 ml, although the volume added varied from 1 ml to 5 ml between different studies. The volume of drug nebulised was estimated from the difference in the volume of drug before and after nebulisation. It was found that approximately 1 ml of sodium chloride (9 g/l, 0.15 mol/l) was nebulised each five minutes. The dose of drug reaching the airways was unknown, although following administration of drugs from pressurised aerosol cannisters only a small proportion (less than 10%) of the dose enters the small airways (Davies, 1975).

The nebuliser head was placed just outside the subject's open mouth during normal tidal breathing, with the subject seated in a draught free room.

Exercise Testing

Exercise testing consisted of steady state running on an inclined treadmill (10^{o}) (Walkertest motorised treadmill, Vitalograph, Buckingham, England) for between five and eight minutes. The treadmill was situated in a draught free room (3.5 x 6.5 metres), the daily temperature of which was always in the range 19 - 22^{o}C. The speed of the treadmill was adjusted so that the patient's pulse rate at the end of the exercise was at least 170 - 180 beats/min. The same setting and duration was used for each test in any one patient, and each exercise test was performed at the same time of day, but on separate days. In any one patient each study was completed within 10 days. The procedure for exercise testing was

explained to each patient prior to testing. All patients had been shown to develop a fall of greater than 20% in FEV_1 post-exercise in the week prior to being included in any exercise study.

Ten patients with extrinsic asthma were exercised in the manner described, following random double blind pre-treatment with two placebos (saline, 9 g/l, 0.15 mol/l) 30 min prior to exercise. There was no significant difference ($t = 0.02$, $P > 0.48$) in the protective effect of pre-treatment with the two placebos on exercise-induced asthma (Figure 4) (Appendix B gives details).

Drugs

Drug solutions used were ipratropium bromide (Boehringer Ingelheim Limited) 1 g/l, 2.4 mmol/l and 0.25 g/l, 0.6 mmol/l; sodium cromoglycate (Fisons Limited) 10 g/l, 19.5 mmol/l; prostaglandin $F_{2\alpha}$ (Upjohn Limited) 0.5 g/l, 1.0 mmol/l; atropine sulphate (Antigen Limited) 5 g/l, 7.1 mmol/l; clemastine hydrogen fumarate (Wander Pharmaceuticals) 1 g/l, 2.1 mmol/l; 0.5 g/l, 1.0 mmol/l; cimetidine (Smith Kline & French Laboratories Limited) 100 g/l, 0.39 mol/l; dopamine hydrochloride (Arnar-Stone Laboratories) 0.2 g/l, 1.0 mmol/l; thymoxamine hydrochloride (W.R. Warner & Company Limited) 0.06 g/l, 189.0 µmol/l; dextrose (Travenol Laboratories Limited) 50 g/l, 0.25 mol/l; sodium chloride (Travenol Laboratories Limited) 9 g/l, 0.15 mol/l.

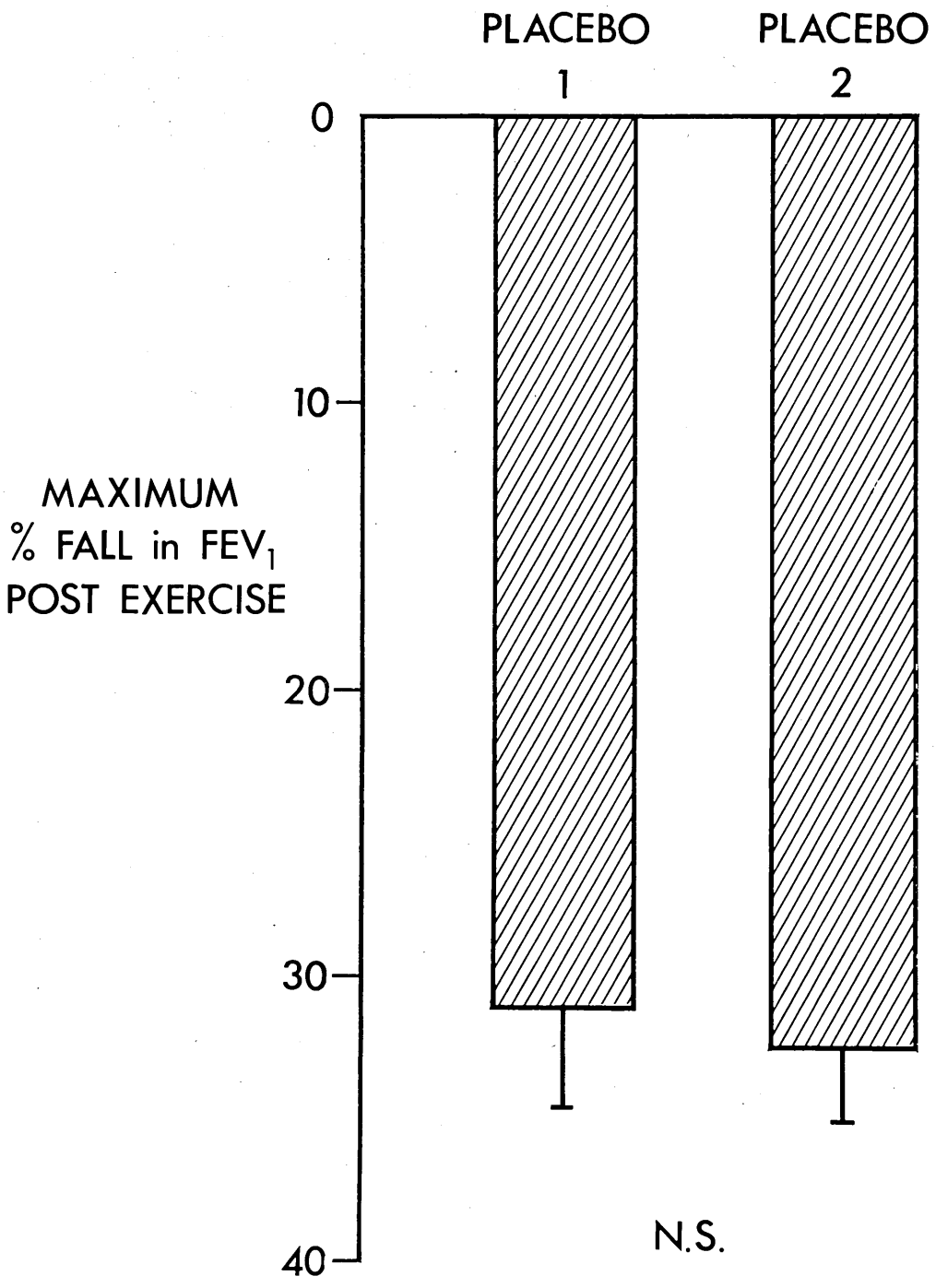

FIGURE 4 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FEV_1 AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING PLACEBO 1 OR PLACEBO 2 IN ASTHMATIC PATIENTS (N = 10)

Powdered bupivacaine hydrochloride (Duncan, Flockhart & Company Limited) was dissolved in water to make a 4% solution (116.6 mmol/l). A solution of citric acid was made up at concentrations of 200 g/l and 100 g/l. Powdered histamine dihydrochloride (Sigma (London) Chemical Company Limited) was dissolved in water to make solutions at concentrations of 50 g/l, 271 mmol/l or less. Powdered methacholine dihydrochloride (Sigma (London) Chemical Company Limited) was dissolved in water to make solutions at concentrations of 50 g/l, 255.0 mmol/l or less. The solutions of histamine dihydrochloride and methacholine dihydrochloride were made up just before each experiment.

Statistical Analysis

In studies with seven or less subjects the statistical significance of observed changes in Raw, Vtg and sGaw was determined using the Fisher, Irwin & Yates exact probability test (Siegal, 1956). In studies with eight or more subjects statistical comparisons of Raw, Vtg and sGaw were made by Wilcoxon matched-pairs signed-rank test (Siegal, 1956). The statistical significance of observed changes in FEV_1, FVC and MMEF was determined by "Student's" paired and unpaired t tests. Differences were considered significant if $P < 0.05$.

CHAPTER III

EFFECT OF H_1 AND H_2 RECEPTOR ANTAGONISTS ON AIRFLOW RESISTANCE

INTRODUCTION

Histamine is released when sensitized human lung tissue interacts with specific antigen *in vitro* (Austen & Orange, 1975). Evidence for histamine acting as a chemical mediator in asthma is based on reports of raised histamine levels following oral aspirin challenge (Stevenson *et al*, 1976), exercise challenge (Ferris *et al*, 1978), allergen challenge (Bhat *et al*, 1976) and spontaneously occurring asthma (Simon *et al*, 1977). In experimental animals histamine has been shown to constrict airway smooth muscle by a direct local effect (Dale & Laidlaw, 1910), and also by a reflex vagal pathway (Gold *et al*, 1972). In patients with asthma, however, histamine acts mainly by direct stimulation of bronchial smooth muscle (Casterline *et al*, 1976; Cockcroft *et al*, 1978; Woenne *et al*, 1978). In other tissues of the body two types of histamine receptor have been identified (Ash & Schild, 1966; Black *et al*, 1972). Smooth muscle contraction is mediated by H_1 receptors, while H_2 receptor responses involve gastric acid secretion and cardiac stimulation. Vasodilation is mediated by both H_1 and H_2 (Black, Owen & Parsons, 1975). Recent *in vitro* studies have indicated that H_1 and H_2 receptors are present in human bronchial smooth muscle (Dunlop & Smith, 1977).

The purpose of this study was to investigate whether H_1 and/or H_2 receptor responses are present in the airways of normal subjects and asthmatic patients.

Methods

Seventeen patients with extrinsic asthma (Table II) and eight normal subjects (three smoked 10 - 15 cigarettes per day) were studied. The mean of six recordings was calculated to give sGaw. FEV_1 was measured in triplicate using a dry wedge spirometer (Vitalograph), the best recording being used for analysis.

All solutions were inhaled through a Wright nebuliser. The subject placed the nebuliser just outside the open mouth and took tidal breaths of the aerosol. The different aerosols were always inhaled by each subject on separate days. Subjects were unaware of the sequence of the aerosols which were randomly assigned. In each subject, tests were performed at the same time of day.

Experimental Procedures

Normal subjects:

In six normal subjects following baseline measurements of sGaw, saline (9 g/l, 0.15 mol/l), clemastine (1 g/l, 2.1 mmol/l) or cimetidine (100 g/l, 0.39 mol/l)was inhaled through a Wright nebuliser for 5 min, sGaw then being recorded at 2, 5, 10, 20, 30 and 60 min.

In eight normal subjects measurements of sGaw were performed before and 30 min after inhaling saline (9 g/l, 0.15 mol/l), clemastine (1 g/l, 2.1 mmol/l) or cimetidine (100 g/l, 0.39 mol/l) for 5 min. Five

TABLE II Clinical details of asthmatic patients

Patient No	Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean Baseline FEV_1 (l)	% Predicted FEV_1
1 L.H.	17	F	160	47	3.24	106.2
2 W.L.	21	M	166	63	4.20	109.0
3 E.B.	31	F	166	56	3.00	98.3
4 A.S.	25	M	190	80	3.82	81.2
5 W.W.	18	M	174	84	4.16	101.4
6 V.D.	26	F	159	62	2.63	87.6
7 C.W.	19	F	152	54	2.23	81.7
8 R.S.	24	M	175	81	4.66	112.2
9 A.B.	36	F	157	64	1.71	63.2
10 S.McK.	17	M	160	63	2.60	72.2
11 F.A.	28	F	175	59	4.13	121.4
12 D.D.	45	M	177	78	4.26	118.3
13 N.B.	24	M	183	75	5.36	120.4
14 F.W.	30	M	165	68	4.01	109.8
15 M.S.	34	M	165	70	2.33	65.6
16 A.O.	34	F	163	73	2.75	94.8
17 P.P.	16	F	156	56	2.57	85.6

breaths of increasing concentrations of histamine dihydrochloride (1.5, 3.1, 6.2, 12.5, 25.0, 50.0 g/l, 271mmol/l) were then inhaled every 3 min, with sGaw recorded at 2 min after each inhalation.

In a separate series of experiments in the same eight subjects, sGaw was measured before and 30 min after inhaling saline (9 g/l, 0.15 mol/l), clemastine (1 g/l, 2.1 mmol/l) or ipratropium bromide (1 g/l, 2.4 mmol/l) for 5 min. Five breaths of increasing concentrations of methacholine dihydrochloride (3.1, 6.2, 12.5, 25.0, 50.0 g/l, 255 mmol/l) were then inhaled every 3 min, with sGaw recorded at 2 min after each inhalation.

Asthmatic patients:

In eight asthmatic patients (Nos 1 - 8) following baseline measurements of FEV_1 saline (9 g/l, 0.15 mol/l) or clemastine (0.5 g/l, 1.0 mmol/l) was inhaled for 5 min, FEV_1 being recorded at 30, 60, 90 and 120 min.

In a further eight asthmatic patients (Nos 3 - 6, 8, 9, 16, 17) following baseline measurements of FEV_1 saline (9 g/l, 0.15 mol/l) or cimetidine (100 g/l, 0.39 mol/l) was inhaled for 5 min, FEV_1 then being recorded at 10, 30, 60, 90 and 120 min.

Finally in eight asthmatic patients (Nos 10 - 17), FEV_1 was measured before and 30 min after inhaling saline (9 g/l, 0.15 mol/l), clemastine (0.5 g/l, 1.0 mmol/l) or cimetidine (100 g/l, 0.39 mol/l)

for 5 min. Five breaths of increasing concentrations of histamine dihydrochloride (0.15, 0.31, 0.62, 1.25, 2.5, 5.0 g/l, 27.1 mmol/l) were then inhaled every 3 min, with FEV_1 recorded at 2 min after each inhalation.

The statistical significance of observed changes in sGaw was determined using the Wilcoxon matched-pairs signed-rank test and Fisher, Irwin & Yates exact probability test (experiment involving six subjects only) and of observed changes in FEV_1 by "Student's" paired t test. Differences were considered significant if $P < 0.05$.

RESULTS

Normal Subjects

In six subjects no significant difference was found in pre-treatment sGaw, or absolute changes in sGaw at 2, 5, 10, 20, 30 and 60 min following the inhalation of clemastine, cimetidine or saline (Table III, Figure 5).

In eight subjects no significant difference was found in pre-treatment sGaw, or absolute changes in sGaw at 30 min following the inhalation of clemastine, cimetidine or saline. The change in sGaw after pre-treatment with clemastine was significantly smaller than the change in sGaw after pre-treatment with saline following 25.0 g/l ($P < 0.05$) and 50.0 g/l ($P < 0.01$) of inhaled histamine or after pre-treatment with cimetidine following 25.0 g/l ($P < 0.05$) and 50 g/l ($P < 0.01$) of inhaled histamine. After pre-treatment with cimetidine and saline there was no significant difference in the

change in sGaw at each dose of inhaled histamine ($P < 0.05$) (Table IV, Figure 6). In the same eight normal subjects, inhaled ipratropium bromide produced a significant rise in sGaw ($P < 0.01$), whereas inhaled clemastine and saline had no effect on sGaw. The change in sGaw after pre-treatment with ipratropium bromide was significantly different from the change in sGaw after pre-treatment with clemastine or saline following 12.5, 25.0 and 50.0 g/l of inhaled methacholine ($P < 0.01$) (Table V, Figure 7).

The effects of the above agents on Raw and Vtg are tabulated in Appendix D, Tables XL - XLVIII.

Asthmatic Patients

In eight asthmatic patients (Nos 1 - 8) inhaled clemastine produced a significant increase in FEV_1 at 60 min ($P < 0.02$), 90 min ($P < 0.02$) and 120 min ($P < 0.05$) after the inhalation (Table VI, Figure 8). The maximum mean % increase in FEV_1 ($\pm$ ISD) after clemastine (14.3 ± 9.7) was significantly greater than after saline (5.7 ± 3.7) ($P < 0.02$). In a separate study on eight asthmatic patients (Nos 3 - 6, 8, 9, 16, 17) there was no significant difference in the absolute change in FEV_1 after pre-treatment with cimetidine or saline at 10, 30, 60, 90 and 120 min after the inhalation (Table VII, Figure 9).

In eight asthmatic patients (Nos 10 - 17) no significant difference was found in pre-treatment FEV_1 or absolute changes in FEV_1 at 30 min following the

inhalation of clemastine, cimetidine or saline. After pre-treatment with cimetidine there was no significant difference in the change in FEV_1 at each dose of inhaled histamine when compared to after pre-treatment with saline. The change in FEV_1 after pre-treatment with clemastine was significantly smaller than the change after pre-treatment with saline following 0.62 g/l ($P < 0.01$), 1.25 g/l ($P < 0.01$), 2.5 g/l ($P < 0.01$) of inhaled histamine or after pre-treatment with cimetidine following 0.31 g/l ($P < 0.02$), 0.62 g/l ($P < 0.05$), 1.25 g/l ($P < 0.02$), 2.5 g/l ($P < 0.01$) of inhaled histamine (Table VIII, Figure 10). Because only three patients were able to inhale histamine at a concentration of 5.0 g/l after pre-treatment with saline or cimetidine statistical comparison with the changes in FEV_1 following pre-treatment with clemastine was not possible, although in each case the changes in FEV_1 after clemastine were much smaller than those after saline or cimetidine. In each of the eight asthmatic patients studied the cumulative log histamine dose response curve was shifted to the right after pre-treatment with clemastine in comparison to after pre-treatment with saline or cimetidine (Figure 11).

DISCUSSION

At least two types of histamine receptor are involved in the histamine response (Ash & Schild, 1966). Clemastine is an extremely potent and specific H_1 receptor antagonist with no central or circulatory effects in conscious animals (Römer & Weidmann, 1966).

It possesses no significant anticholinergic or antiserotonin activity (Weidmann et al, 1967; Kallós, 1971). The concentration of clemastine inhaled by the asthmatics was half that administered to the normal subjects, since a concentration of greater than 0.5 g/l was found to produce upper airway irritation. H_2 receptor responses are blocked by burimamide, metiamide and cimetidine but not by H_1 receptor antagonists clemastine and chlorpheniramine (Black et al, 1972). Cimetidine is a specific competitive H_2 receptor antagonist with no significant interaction at catecholamine β -receptors, H_1 receptors or muscarinic receptors (Parsons, 1977). The concentration of cimetidine used in this study has been shown to effectively inhibit H_2 responses such as gastric acid secretion in humans (Hirschowitz, 1979).

The absence of any significant change in airways calibre of normal subjects after an inhaled H_1 receptor antagonist suggests that this receptor is not important in the maintenance of normal airways tone. Several H_1 receptor antagonists, however, have been reported to cause bronchodilation in asthmatic patients. Popa (1977) found increases in the airways calibre of 10 asthmatic patients after intravenously administered chlorpheniramine (10 mg) although this was complicated by drowsiness in several subjects. Nogrady et al, (1978) reported that inhaled clemastine produced a maximum percentage increase in FEV_1 of 21% in 12 asthmatic patients, in comparison to an increase of 14% found in this study. Although the

dose and method of administration of clemastine were similar, the better baseline function of the patients in the present study may account for the smaller increase in FEV_1 after clemastine. The reason for the difference in response to an inhaled H_1 antagonist between normal subjects and patients with asthma is unexplained but may indicate continuous release of histamine in the asthmatic group as has recently been suggested (Nogrady & Bevan, 1978).

In experimental animals, histamine acts locally on the airway smooth muscle causing constriction (Dale & Laidlaw, 1910) and can also stimulate vagal irritant receptors in the airways causing reflex bronchoconstriction (Gold et al, 1972). In normal subjects and patients with asthma, however, the main site of action of histamine is probably by direct stimulation of human bronchial smooth muscle (Casterline et al, 1976; Cockcroft et al, 1978; Woenne et al, 1978; Chapter IV), via H_1 and/or H_2 receptors. The protective action of the H_1 receptor antagonist clemastine on histamine-induced bronchoconstriction in asthmatic subjects confirms the findings of Nogrady & Bevan (1978) and extends this observation to normal subjects. These findings, therefore, suggest that histmaine was acting at the H_1 receptor in both normal subjects and asthmatic patients. A similar reduction in bronchoconstrictor effect of histamine has also been reported with less potent (Woenne et al, 1978; Eiser, Guz & Snashall, 1978[a]) or specific (Casterline & Evans, 1977) H_1 receptor

antagonists than clemastine. H_1 receptor antagonists may possess to a variable degree anticholinergic and local anaesthetic effects (Douglas, 1975). In the present study, clemastine had no significant anticholinergic action in normal subjects and it has been shown to have no protective effect on methacholine induced bronchostriction in asthmatics (Nogrady & Bevan, 1978). A local anaesthetic effect by clemastine on sensory irritant receptors is also unlikely. Firstly, anticholinergic drugs only slightly reduce the airway response to histamine in comparison to H_1 receptor antagonists (Casterline et al, 1976; Cockcroft et al, 1978; Woenne et al, 1978; Chapter IV). Secondly, the inhaled local anaesthetic bupivacaine has no preventive action on histamine induced bronchoconstriction in normal subjects (Chapter IV). Changes in baseline airflow obstruction may alter bronchial reactivity (Benson, 1975). This is unlikely, however, to be relevant to the present study, since although clemastine causes bronchodilation in asthmatic patients, this was only slight at 30 min following inhaled clemastine when histamine challenge was performed. Furthermore, in normal subjects clemastine displaced the histamine dose response curve when there was no change in baseline lung function. The most likely explanation for these findings is that there are H_1 receptors in human airways.

The present results do not support the hypothesis that H_2 receptors are present in the airways of normal

subjects and asthmatics (Busse & Sosman, 1977). Slight changes in small airways function, however, could have been missed by measurement of specific conductance in normal subjects and FEV_1 in asthmatic patients. Eyre (1973) showed that the relaxant effect of histamine on sheep terminal bronchus was an H_2 response. In atopic and non-atopic human subjects, however, inhaled histamine causes bronchoconstriction of both large and small airways (Brown et al, 1977). It is unknown whether the dose of cimetidine inhaled in this study was sufficient to produce complete H_2 receptor blockade, although a similar concentration of cimetidine has been shown to effectively inhibit other human H_2 responses (Hirschowitz, 1979). The inhalation technique used to give cimetidine and histamine should have resulted in a similar degree of aerosol deposition within the airways, even if their sites of action were different. There are differences between cimetidine and other H_2 receptor blockers in their ability to reduce mediator release from sensitized tissue (Drazen, Venugopalan & Soter, 1978). These authors found that burimamide and metiamide but not cimetidine increased the anaphylactic reactions in sensitized guinea pigs. It is unknown whether any possible difference between cimetidine and other H_2 receptor blockers would be relevant to the identifications of human bronchial smooth muscle H_2 receptors. Finally, in some experimental systems, H_2 antagonists have no effect alone, but act synergistically when combined with H_1

antagonists (Powell & Brody, 1976). A similar synergistic action in bronchial smooth muscle cannot be excluded from this study.

If histamine is shown to be an important mediator of immediate type hypersensitivity in human asthma, then the predominant site of action of histamine is probably by a direct effect on bronchial smooth muscle H_1 receptors.

TABLE III Effect of inhaled clemastine, cimetidine and saline on sGaw in normal subjects (N = 6)

Subjects		Pretreatment			sGaw(s^{-1}k Pa^{-1}) Time after inhalation (min) 2			5			10			20			30			60		
Age	Sex	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.
IW 36	M	1.34	1.07	0.87	1.49	1.50	0.99	1.62	1.16	0.97	1.62	1.18	1.02	1.46	1.15	0.89	1.50	1.14	0.97	1.18	1.10	1.00
RJ 22	F	2.48	2.02	2.12	2.21	1.81	2.47	2.15	1.84	2.22	2.56	1.92	2.39	2.49	1.92	2.54	2.15	1.79	2.40	2.37	2.20	2.30
NT 30	M	1.89	1.67	2.15	1.63	1.86	1.97	1.54	1.97	2.12	1.67	1.73	1.78	1.97	1.71	1.66	2.25	1.49	1.91	2.14	1.50	1.98
DI 26	M	0.77	0.79	0.55	0.74	0.63	0.71	0.78	0.70	0.66	0.66	0.72	0.66	0.64	0.70	0.76	0.66	0.77	0.65	0.62	0.99	0.63
KC 25	M	0.89	0.75	0.93	0.99	0.84	0.77	0.99	0.93	0.80	1.04	1.08	0.88	0.87	0.96	0.90	0.76	0.95	0.75	0.87	0.93	0.81
AL 24	F	1.68	1.69	1.60	1.85	1.58	1.54	1.90	1.55	1.44	1.72	1.53	1.48	1.62	1.50	1.50	1.58	1.52	1.43	1.72	1.48	1.40
Mean		1.50	1.33	1.37	1.48	1.37	1.41	1.49	1.36	1.37	1.54	1.36	1.37	1.51	1.32	1.37	1.48	1.28	1.35	1.48	1.37	1.35
SEM		0.26	0.21	0.28	0.22	0.21	0.29	0.21	0.21	0.27	0.26	0.18	0.26	0.28	0.19	0.28	0.27	0.16	0.28	0.29	0.19	0.27

Clemastine (Clem.); cimetidine (Cim.); saline (Sal.)

* Values significantly different from those after saline at that time ($P < 0.05$)

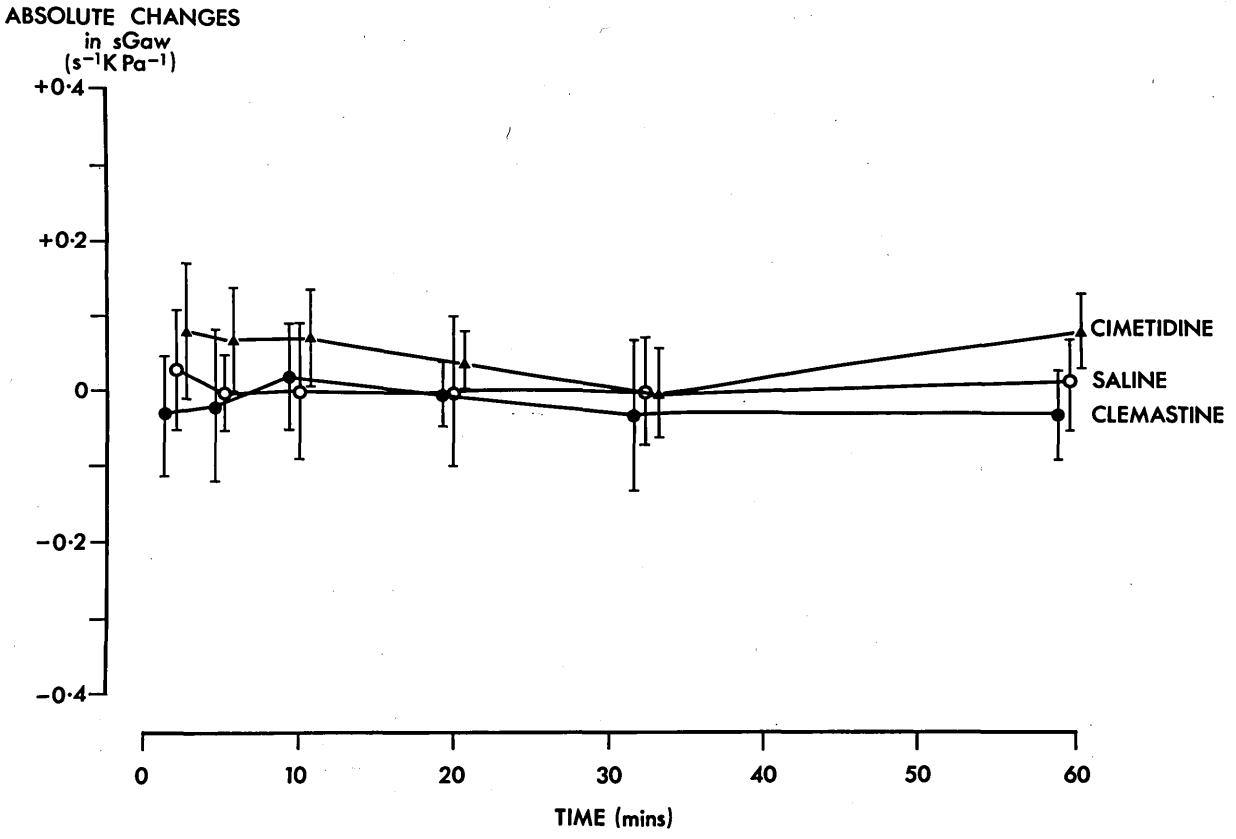

FIGURE 5 EFFECT OF INHALED CLEMASTINE, CIMETIDINE AND SALINE ON ABSOLUTE CHANGE IN sGaw IN NORMAL SUBJECTS (N = 6)

TABLE IV Effect of inhaled histamine on sGaw following clemastine, cimetidine or saline in normal subjects (N = 8)

Subject			Baseline sGaw ($s^{-1}kPa^{-1}$)						Conc. of histamine (g/l)						Change in sGaw											
			B			A			1.5			3.1			6.2			12.5			25.0			50.0		
	Age	Sex	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.
IW	36	M	0.86	0.99	1.29	1.01	0.92	1.34	+0.10	-0.05	-0.21	-0.04	-0.12	-0.23	-0.03	-0.19	-0.35	-0.11	-0.31	-0.55	-0.20	-0.39	-0.66	-0.41	-0.39	-0.74
RJ	22	F	1.90	1.50	1.61	1.83	1.60	1.63	+0.62	+0.10	-0.10	+0.56	+0.22	+0.04	+0.63	-0.08	-0.27	+0.55	-0.16	-0.34	+0.58	-0.76	-0.75	+0.33	-1.09	-0.96
NT	30	M	1.85	1.74	1.63	1.87	1.71	1.47	+0.03	+0.11	+0.03	-0.16	+0.05	+0.01	+0.26	+0.10	+0.23	-0.33	-0.49	-0.20	+0.07	-0.54	-0.41	-0.52	-1.07	-0.81
AL	24	F	1.99	2.32	2.51	1.87	2.12	1.78	+0.16	-0.24	-0.03	+0.25	-0.21	+0.14	+0.08	-0.44	+0.10	+0.45	-0.07	-0.04	+0.40	-0.42	+0.03	+0.08	-1.03	-0.50
MK	26	F	1.16	1.13	0.96	1.13	0.90	0.92	-0.11	+0.05	+0.24	-0.08	-0.03	+0.20	-0.01	+0.16	+0.18	+0.13	-0.07	+0.13	-0.30	-0.24	-0.36	-0.32	-0.56	-0.67
DI	26	M	0.77	0.76	0.70	0.69	0.79	0.75	+0.04	-0.03	+0.12	+0.19	-0.04	+0.13	+0.04	+0.05	+0.10	+0.04	+0.04	-0.08	+0.12	-0.17	-0.26	-0.02	-0.50	-0.44
AMcF	23	F	1.61	1.65	1.68	1.72	1.73	1.70	-0.48	-0.35	-0.11	-0.62	-0.48	-0.24	-0.50	-0.68	-0.78	-0.87	-1.09	-1.21	-0.98	-1.25	-1.33	-1.25	-1.38	-1.36
KC	25	M	1.30	1.21	1.30	1.48	1.34	1.48	-0.11	-0.25	-0.31	-0.17	-0.39	-0.41	-0.36	-0.51	-0.53	-0.38	-0.58	-0.61	-0.43	-0.65	-0.74	-0.44	-0.71	-0.79
Mean			1.43	1.41	1.46	1.45	1.38	1.38	+0.03	-0.08	-0.04	-0.00	-0.12	-0.04	-0.00	-0.19	-0.16	-0.06	-0.34	-0.36	-0.09*	-0.55	-0.56	-0.31**	-0.84	-0.78
SEM			0.16	0.17	0.19	0.16	0.16	0.13	0.10	0.06	0.06	0.12	0.08	0.07	0.12	0.10	0.13	0.16	0.13	0.15	0.17	0.12	0.14	0.16	0.12	0.10

B, before pretreatment; A, after clemastine (Clem.), cimetidine (Cim.), or saline (Sal.)

Values significantly different from those with saline pretreatment at that concentration * $p < 0.05$, ** $p < 0.01$

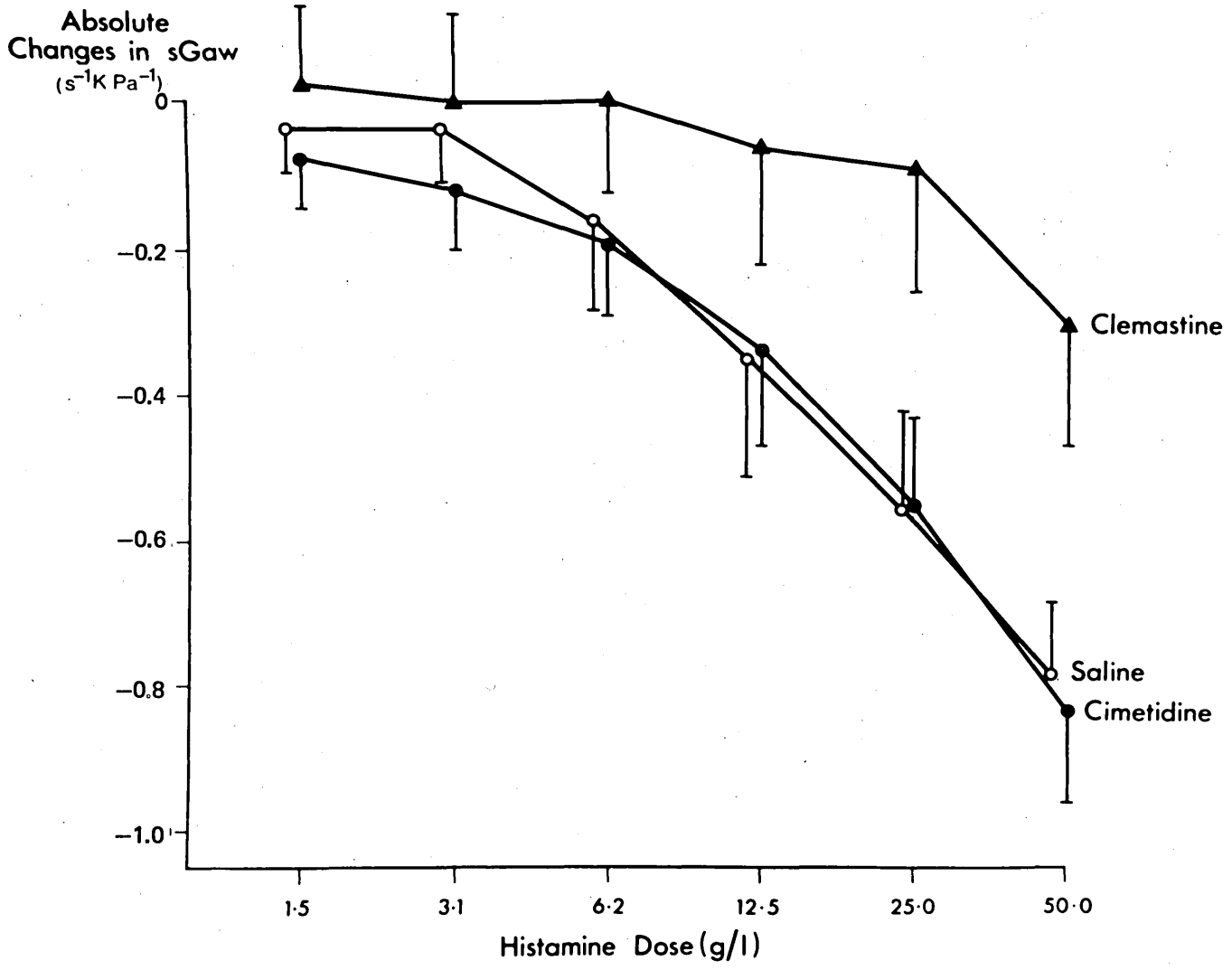

FIGURE 6 ABSOLUTE CHANGE IN sGaw PLOTTED AGAINST CUMULATIVE LOG DOSE OF INHALED HISTAMINE IN NORMAL SUBJECTS (N = 8) FOLLOWING PRETREATMENT WITH CLEMASTINE, CIMETIDINE OR SALINE

TABLE V Effect on sGaw of inhaled methacholine following inhaled ipratropium, clemastine or saline in normal subjects (N = 8)

Subject	Age	Sex	Baseline sGaw ($s^{-1}kPa^{-1}$) B IB	B Clem.	B Sal.	A IB	A Clem.	A Sal.	Conc. of methacholine (g/l)	Change in sGaw 3.1 IB	3.1 Clem.	3.1 Sal.	6.2 IB	6.2 Clem.	6.2 Sal.	12.5 IB	12.5 Clem.	12.5 Sal.	25.0 IB	25.0 Clem.	25.0 Sal.	50.0 IB	50.0 Clem.	50.0 Sal.
IW	36	M	0.85	1.12	0.87	1.15	1.29	1.07		+0.03	-0.20	+0.02	+0.07	-0.16	-0.15	+0.10	-0.20	-0.27	+0.15	-0.38	-0.45	+0.13	-0.54	-0.48
RJ	22	F	2.28	2.74	2.83	3.27	2.87	2.63		+0.24	-0.50	-0.45	+0.06	-1.00	-1.09	-0.20	-1.84	-1.67	+0.22	-2.39	-2.07	-0.10	-2.40	-2.21
NT	30	M	2.75	2.01	2.05	3.18	2.37	2.18		-0.05	-0.40	-0.02	+0.17	+0.02	+0.34	+0.03	-0.65	+0.00	-0.29	-0.66	-0.34	-0.33	-1.03	-0.98
AL	24	F	1.65	1.83	1.80	1.95	1.80	1.75		+0.18	-0.02	+0.09	+0.13	+0.12	-0.02	-0.09	-0.03	-0.15	-0.11	-0.29	-0.43	-0.20	-0.98	-0.69
MK	26	F	1.05	1.05	1.15	1.35	1.02	1.30		-0.20	+0.10	+0.13	+0.03	-0.02	-0.10	-0.14	-0.25	-0.21	-0.16	-0.58	-0.52	-0.02	-0.68	-0.97
DI	26	M	0.75	0.75	0.80	0.96	0.80	0.85		-0.18	-0.09	-0.01	-0.09	-0.09	+0.15	+0.07	-0.13	-0.10	-0.12	-0.63	-0.56	-0.18	-0.69	-0.68
AMcF	23	F	1.78	1.53	1.60	2.25	1.70	1.55		-0.03	+0.10	-0.02	-0.09	-0.13	-0.08	-0.15	-0.18	-0.23	+0.20	-0.50	-0.63	+0.30	-0.82	-0.70
KC	25	M	1.40	1.30	1.30	1.80	1.15	1.37		-0.08	-0.13	+0.10	-0.15	-0.15	-0.12	-0.19	-0.38	-0.41	-0.05	-0.72	-0.62	-0.13	-0.75	-0.80
Mean			1.56	1.54	1.55	1.98	1.62	1.58		-0.01	-0.14	-0.02	+0.01	-0.17	-0.13	-0.07**	-0.45	-0.38	-0.02**	-0.76	-0.70	-0.06**	-1.01	-0.96
SEM			0.24	0.22	0.23	0.30	0.25	0.21		0.05	0.07	0.06	0.04	0.12	0.14	0.04	0.20	0.18	0.06	0.23	0.19	0.07	0.20	0.18

B, before pretreatment; A, after ipratropium bromide (IB), clemastine (Clem.), or saline (Sal.)

** Values significantly different from those with saline pretreatment at that concentration ($p < 0.01$)

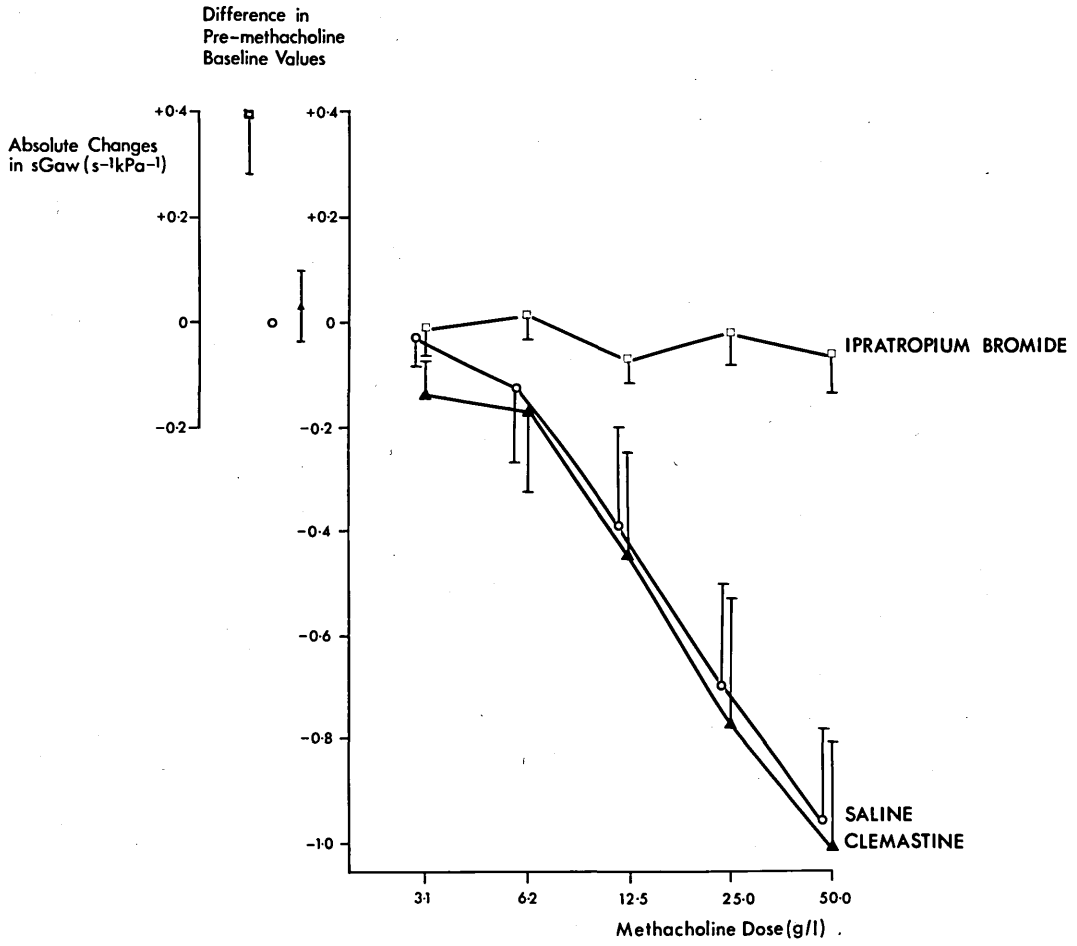

FIGURE 7 ABSOLUTE CHANGE IN sGaw PLOTTED AGAINST CUMULATIVE LOG DOSE OF INHALED METHACHOLINE IN NORMAL SUBJECTS (N = 8) FOLLOWING PRETREATMENT WITH CLEMASTINE, IPRATROPIUM OR SALINE

TABLE VI Effect of inhaled clemastine and saline on FEV_1 in asthmatic patients (N = 8)

Patient No	Baseline FEV_1 (l)		Time after inhalation of saline or clemastine (min)							
			30		60		90		120	
	Sal.	Clem.	Sal.	Clem.	Sal.	Clem.	Sal.	Clem.	Sal.	Clem.
1	3.31(108.5)	3.18(104.2)	+0.07	-0.03	+0.05	+0.02	-0.03	+0.10	+0.09	+0.03
2	4.45(115.5)	3.95(102.5)	-0.13	+0.57	+0.07	+0.80	+0.00	+1.10	+0.20	+0.80
3	3.08(100.9)	2.98(97.7)	+0.10	+0.16	+0.10	+0.20	+0.07	+0.20	+0.10	+0.27
4	3.88(82.5)	3.64(77.4)	+0.00	+0.00	+0.24	+0.37	+0.00	+0.53	+0.44	+0.69
5	4.02(98.0)	4.42(107.8)	+0.03	-0.02	+0.03	-0.07	+0.03	+0.00	+0.03	+0.00
6	2.41(80.3)	2.71(90.3)	+0.17	+0.38	+0.20	+0.63	+0.20	+0.64	+0.23	+0.64
7	2.39(77.0)	2.28(80.0)	+0.12	+0.10	+0.22	+0.35	+0.19	+0.23	+0.15	+0.41
8	4.85(116.8)	4.35(104.8)	+0.07	+0.25	+0.13	+0.48	+0.14	+0.53	+0.25	+0.62
Mean	3.54(97.4)	3.50(95.5)	+0.03	+0.17	+0.03	+0.34	+0.07	+0.41	+0.18	+0.43
SEM	0.32(5.6)	0.30(4.1)	0.03	0.17	0.02	0.10	0.03	0.12	0.04	0.10
t				1.48		2.91		2.66		2.18
P value				NS		<0.02		<0.02		<0.05

Saline (Sal.); Clemastine (Clem.)

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

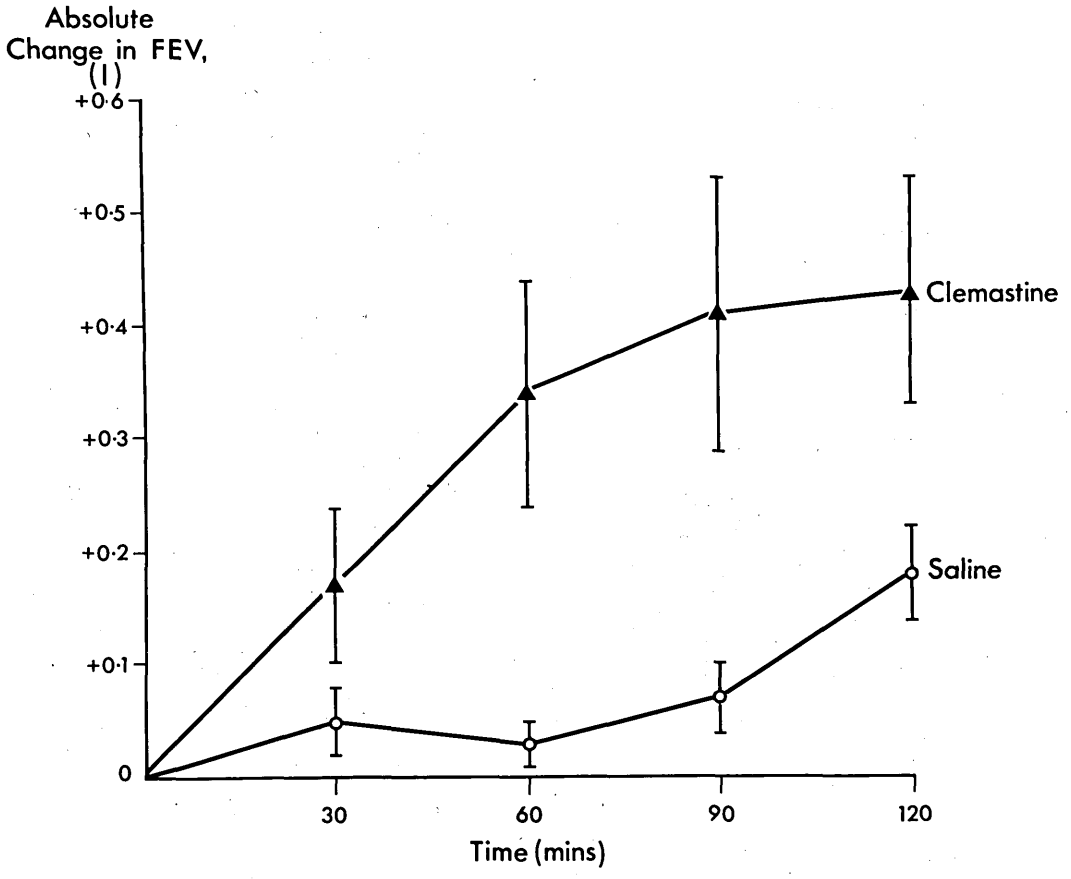

FIGURE 8 EFFECT OF INHALED CLEMASTINE AND SALINE ON ABSOLUTE CHANGE IN FEV_1 IN ASTHMATIC PATIENTS (N = 8)

TABLE VII Effect of inhaled cimetidine and saline on FEV_1 in asthmatic patients (N = 8)

Patient No	Baseline FEV_1 (l)		Time after inhalation of saline or cimetidine (min)									
			10		30		60		90		120	
	Sal.	Cim.	Sal.	Cim.	Sal.	Cim.	Sal.	Cim.	Sal.	Cim.	Sal.	Cim.
3	2.51(83.6)	2.51(83.6)	+0.10	+0.23	+0.20	+0.10	+0.13	+0.17	+0.11	+0.17	+0.11	+0.19
4	2.98(102.7)	2.61(90.0)	+0.00	+0.10	+0.00	+0.03	+0.00	+0.24	+0.00	+0.19	+0.00	+0.22
5	1.77(65.5)	1.66(61.4)	-0.03	-0.12	-0.05	-0.05	-0.06	+0.00	-0.04	+0.02	-0.00	+0.04
6	3.00(98.3)	2.95(96.7)	+0.02	+0.02	+0.03	+0.02	+0.10	+0.05	+0.18	+0.07	+0.18	+0.10
8	3.90(82.9)	3.88(82.5)	+0.00	+0.02	+0.03	+0.02	+0.02	+0.04	+0.08	+0.07	+0.10	+0.09
9	4.20(102.4)	4.02(98.0)	+0.00	+0.03	+0.05	+0.03	+0.03	+0.03	+0.07	+0.03	+0.10	+0.03
16	4.60(110.8)	4.85(116.8)	+0.03	-0.05	+0.10	-0.03	+0.11	-0.02	+0.14	+0.00	+0.15	+0.03
17	2.68(89.3)	2.75(89.3)	+0.05	+0.03	+0.07	+0.03	+0.04	+0.03	+0.04	+0.05	+0.08	+0.07
Mean	3.20(91.9)	3.15(89.7)	+0.02	+0.03	+0.05	+0.01	+0.04	+0.06	+0.07	+0.07	+0.09	+0.09
SEM	0.33(5.1)	0.36(5.5)	0.01	0.03	0.02	0.01	0.02	0.03	0.02	0.02	0.02	0.02
t				0.40		1.84		0.56		0.06		0.16
P value				NS		NS		NS		NS		NS

Saline (Sal.); Cimetidine (Cim.)

Baseline data are expressed as absolute values (1) and percentage of predicted (brackets)

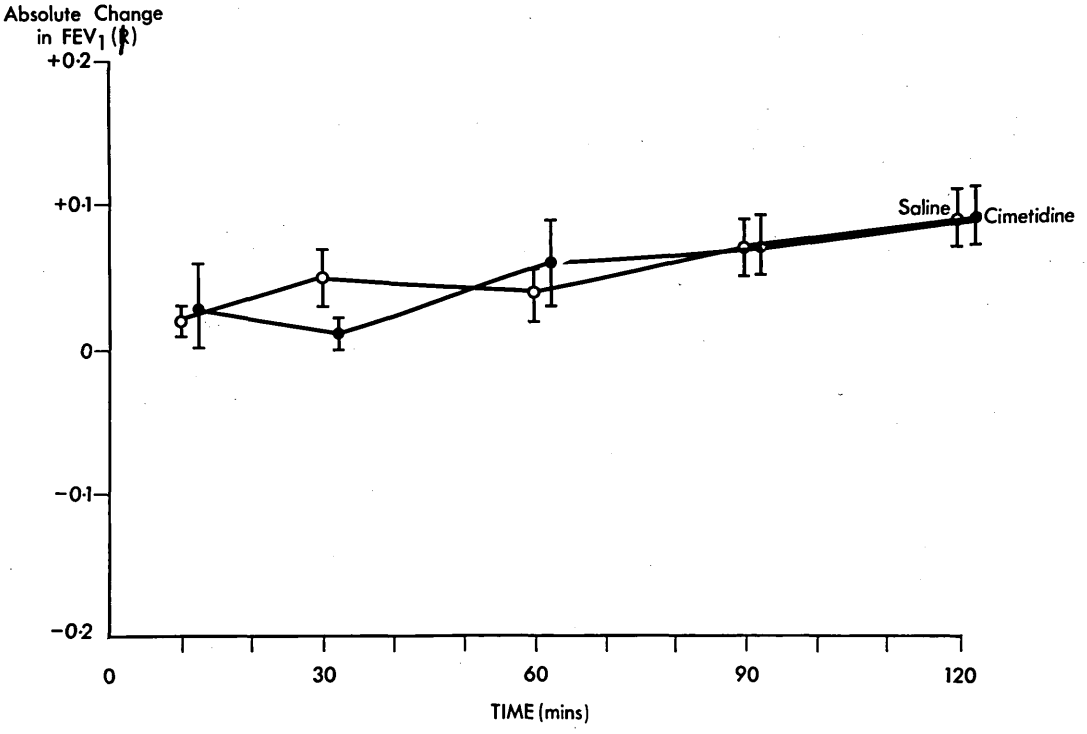

FIGURE 9 EFFECT OF INHALED CIMETIDINE AND SALINE ON ABSOLUTE CHANGE IN FEV_1 IN ASTHMATIC PATIENTS (N = 8)

TABLE VIII Effect of inhaled histamine on FEV_1 following clemastine, cimetidine or saline in asthmatic patients (N=8)

Patient No	Baseline FEV_1 (l)						Change in FEV_1																	
	B			A			Conc. of histamine (g/l) 0.15			0.31			0.62			1.25			2.5			5.0		
	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.	Clem.	Cim.	Sal.
1	2.65	2.60	2.55	2.65	2.75	2.55	-0.10	-0.40	-0.20	-0.05	-0.60	-0.45	-0.05	-0.70	-0.80	-0.15	-1.35	-1.05	-0.25	-1.65	-1.55	-0.30		
2	4.10	4.20	4.10	4.15	4.10	4.10	-0.05	+0.00	-0.10	-0.05	+0.00	-0.10	-0.05	+0.00	-0.35	-0.15	-0.10	-0.50	-0.05	-0.35	-0.90	-0.10	-1.00	-1.50
3	4.10	4.35	4.35	4.40	4.40	4.40	-0.15	-0.55	-0.40	-0.20	-0.90	-0.70	-0.50	-1.60	-1.25	-0.80	-2.10	-2.10	-1.45			-1.75		
4	5.40	5.00	5.70	5.75	5.10	5.60	+0.00	-0.20	+0.15	+0.05	-0.20	+0.00	+0.00	-0.15	-0.20	+0.05	-0.30	-0.45	+0.05	-0.90	-1.35	+0.15	-1.95	-2.35
5	3.85	4.10	4.10	3.95	4.05	4.10	-0.25	-0.05	+0.10	-0.10	-0.55	+0.00	-0.35	-1.05	-0.35	-0.65	-1.80	-1.25	-1.65	-2.53	-2.55	-2.50		
6	2.23	2.25	2.52	2.75	2.30	2.65	+0.05	-0.90	-0.45	-0.05	-1.00	-1.00	-0.20		-1.10	-0.55			-0.65			-0.90		
7	2.75	2.65	2.80	2.85	2.70	2.80	-0.05	-0.05	-0.12	-0.05	-0.25	-0.28	-0.10	-0.45	-0.50	-0.10	-0.85	-0.78	-0.15	-1.35	-1.30	-0.15		
8	2.60	2.65	2.60	2.80	2.70	2.65	-0.05	-0.05	-0.05	+0.00	-0.05	-0.05	-0.05	+0.00	-0.15	-0.20	-0.25	-0.55	-0.15	-0.85	-0.80	-0.25	-1.20	-1.10
Mean	3.46	3.47	3.59	3.66	3.51	3.60	-0.07	-0.27	-0.13	-0.05	-0.44	-0.32	-0.16**	-0.56	-0.58	-0.31**	-0.96	-0.95	-0.53**	-1.27	-1.40	-0.72	-1.38	-1.65
SEM	0.38	0.36	0.40	0.38	0.36	0.39	0.03	0.11	0.07	0.02	0.13	0.13	0.06	0.22	0.14	0.10	0.30	0.22	0.23	0.31	0.25	0.33	0.28	0.36

B, before pre-treatment; A, after clemastine (Clem.), cimetidine (Cim.), or saline (Sal.)

** Values significantly different from those with saline pre-treatment at that concentration ($p < 0.01$)

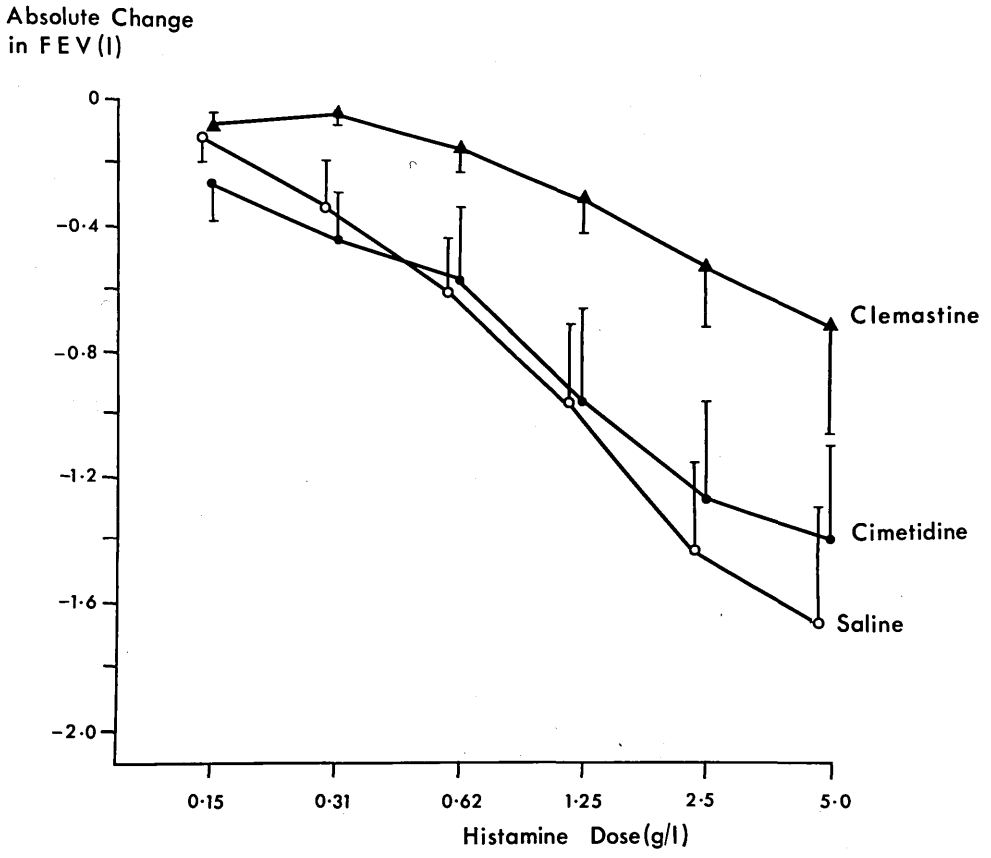

FIGURE 10 ABSOLUTE CHANGE IN FEV_1 PLOTTED AGAINST CUMULATIVE LOG DOSE OF INHALED HISTAMINE IN ASTHMATIC PATIENTS (N = 8) FOLLOWING PRETREATMENT WITH CLEMASTINE, CIMETIDINE OR SALINE

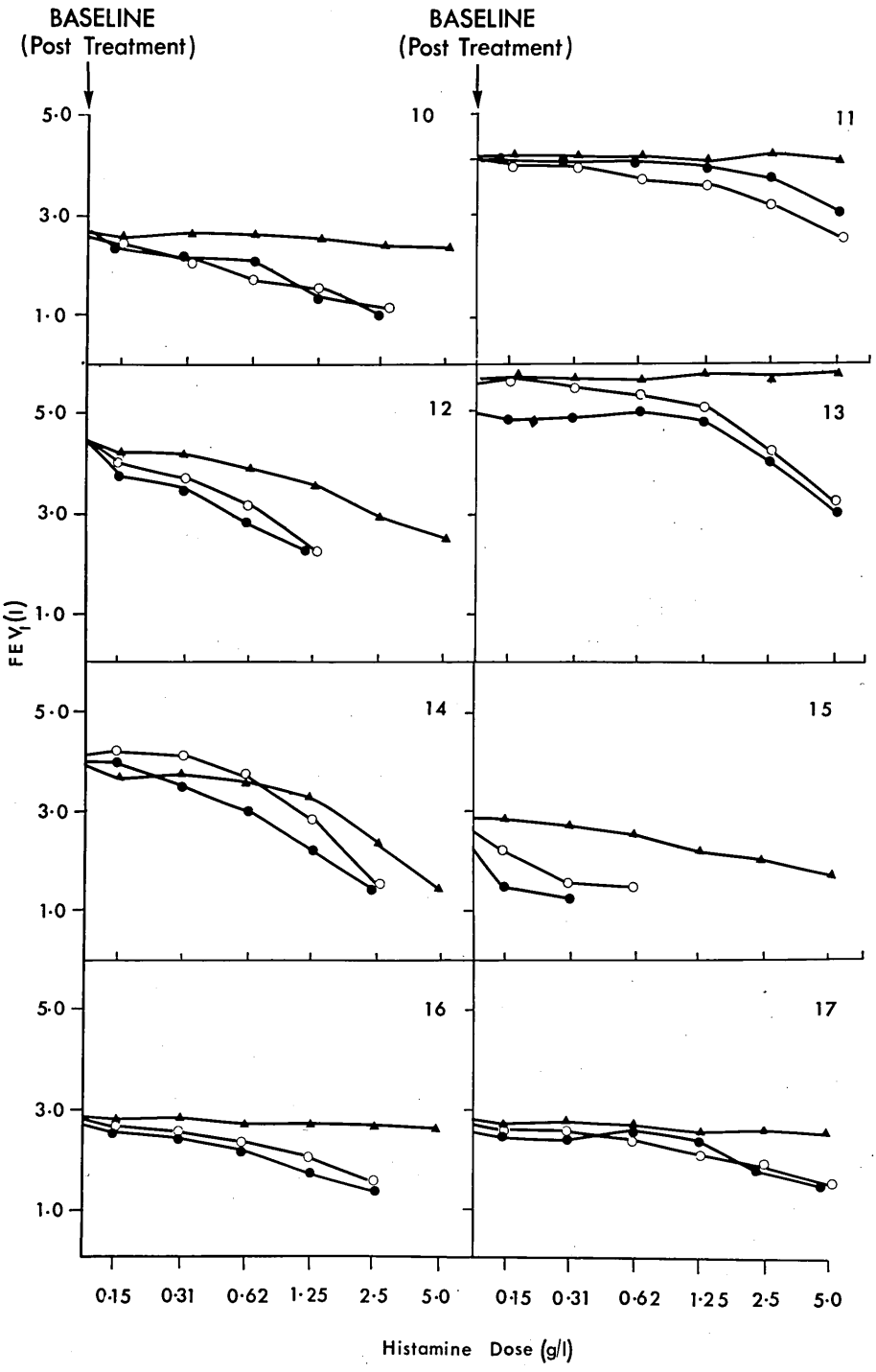

FIGURE 11 ABSOLUTE VALUES FOR FEV_1 PLOTTED AGAINST CUMULATIVE LOG DOSE OF INHALED HISTAMINE FOR EACH OF THE EIGHT ASTHMATIC PATIENTS STUDIED. VALUES FOR FEV_1 ARE SHOWN FOLLOWING PRETREATMENT WITH CLEMASTINE (▲) CIMETIDINE (●) OR SALINE (O)

CHAPTER IV

EFFECT OF DOPAMINE ON AIRFLOW RESISTANCE

INTRODUCTION

Dopamine is a naturally occurring catecholamine which is the immediate precursor of noradrenaline (Blaschko, 1957), and it has been suggested that it acts as an important neurotransmitter in the peripheral autonomic nervous system (Thorner, 1975). Dopamine stimulates adenosine 3' : 5' monophosphate (cyclic AMP) synthesis in postsynaptic ganglia causing hyperpolarisation, which is associated with an increase in the threshold of excitability (Greengard, 1976). This modulating effect of dopamine on autonomic ganglia could thus indirectly effect bronchial smooth muscle tone. Furthermore, Newman Taylor et al, (1976) reported an improvement in pulmonary function in patients with chronic asthma who were treated with the specific dopamine receptor agonist bromocriptine.

Specific dopamine receptors have been identified in renal, mesenteric, coronary and intra-cerebral arterial vascular beds (Goldberg, 1972; Von Essen, 1972), which when stimulated by dopamine cause vasodilation. It is unknown whether such receptors exist in the human bronchial tree, although recently Key et al (1978) reported finding specific dopamine receptors in canine bronchial smooth muscle. Dopamine has been found in significant amounts in the lung of ruminants (Von Euler & Lishajko, 1957), and this lung dopamine has been located in the mast cells (Falck, et al, 1964). Its release from isolated calf lung sensitized with horse serum by specific antigen and by compound 48/80

suggests that, at least in this species, it may be important in immediate type allergy (Eyre & Deline, 1971).

This study was undertaken to evaluate the effects of dopamine on airflow resistance in normal subjects and asthmatic patients.

METHODS

Twelve asthmatic patients with extrinsic asthma (Table IX) and nine normal subjects were studied. FEV_1 was measured in triplicate on a dry wedge spirometer (Vitalograph) at the start of each study day, the best recording being used for analysis. The mean of four recordings was calculated to give sGaw. Radial pulse rate and blood pressure in supine position were measured 1 min before each measurement of sGaw during infusion studies. In each subject tests were performed at the same time of day.

Dopamine by Infusion

With the subject in a supine position, a "Butterfly" No. 19 1.1 mm needle (Abbott Ireland Limited) was inserted into an anticubital fossa vein and connected to a measured volume administration set - "Metriset" (AHS/UK Henleys Medical Supplies Limited).

In six normal subjects following baseline measurements, an infusion of dopamine (0.2 g/l, 1.0 mmol/l) in dextrose (50 g/l, 0.25 mol/l) was commenced

TABLE IX Clinical details of asthmatic patients

Patient No	Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean Baseline FEV_1 (l)	% Predicted FEV_1
1 M.O'D.	24	F	156	53	2.80	94.9
2 A.McN.	19	F	170	61	3.40	103.0
3 T.K.	18	F	161	55	2.95	95.2
4 M.W.	18	F	151	45	2.85	101.7
5 M.S.	30	M	176	61	3.65	90.1
6 A.H.	32	M	186	79	4.0	90.9
7 A.A.	18	M	173	64	4.3	104.8
8 J.H.	27	F	159	54	2.75	91.6
9 B.McL.	18	M	168	68	4.00	105.2
10 A.H.	24	F	150	48	2.60	92.8
11 S.S.	29	F	158	51	2.20	75.8
12 J.C.	21	M	165	69	3.65	96.0

at a rate of 5 μg $Kg^{-1}min^{-1}$ for 10 min. The infusion was then stopped and measurements made at 1, 5, 10, 15 and 20 min. In eight asthmatic patients (Nos 1 - 8) following initial measurements, a placebo infusion of dextrose (50 g/l, 0.25 mol/l) was commenced and after 10 min they were disconnected from the infusion and baseline measurements repeated. The patients were then reconnected to the infusion and without the subject's knowledge, dopamine (0.2 g/l, 1.0 mmol/l) in dextrose (50 g/l, 0.25 mol/l) was substituted and infused at a rate of 5 μg $Kg^{-1}min^{-1}$ for 10 min. The patients were again disconnected from the infusion and measurements made at 1, 5, 10 and 20 min, dextrose (50 g/l, 0.25 mol/l) being infused between these measurements.

Six of the asthmatic patients (Nos 3 - 8) were given an additional infusion of thymoxamine (0.06 g/l, 189.0 μmol/l) in dextrose (50 g/l, 0.25 mol/l) for 10 min at a rate of 0.1 mg min^{-1} which was then continued in combination with dopamine (0.2 g/l, 1.0 mmol/l) in dextrose (50 g/l, 0.25 mol/l) at a rate of 5 μg $Kg^{-1}min^{-1}$ for a further 10 min. sGaw was measured prior to each infusion and at 1 and 5 min after the combined infusion.

Dopamine by Inhalation

In six normal subjects following baseline measurements, a saline solution (0.9 g/l, 0.15 mol/l) was inhaled through a Wright nebuliser for 2 min and sGaw recorded 1 min after the inhalation. After a

further 4 min dopamine (0.5 g/l, 2.6 mmol/l) was inhaled for 2 min and sGaw recorded 1 min later. If no change in airways calibre was observed the dose of dopamine inhaled was increased to 1 g/l (5.2 mmol/l) and then to 2 g/l (10.5 mmol/l) and sGaw measurements repeated at similar time intervals. A similar protocol was used in six asthmatic patients (Nos 2, 7, 9 - 12).

The statistical significance of observed changes in sGaw was determined by the Wilcoxon matched-pairs signed-rank test in experiments involving eight subjects and by the Fisher Irwin and Yates exact probability test in experiments involving six subjects. Differences were considered significant if $P < 0.05$.

RESULTS

Bronchial Response to Dopamine by Infusion

No significant changes in sGaw were seen in normal subjects or in patients with asthma following the infusion of dopamine (Table X, Figure 12). The six asthmatic patients who received the combined infusion of thymoxamine and dopamine showed no significant changes in sGaw compared to thymoxamine alone (Table XI, Figure 13). In both groups of subjects, pulse and blood pressure remained unchanged during the study period (Figures 14, 15). No side effects were noted by any subjects.

The effects of infused dopamine alone or in

combination with thymoxamine on Raw, Vtg, radial pulse rate, systolic and diastolic blood pressure in normal subjects and asthmatic patients are tabulated in Appendix D, Tables XLIX - LIV.

Bronchial Response to Dopamine by Inhalation

(Table XII, Figure 16). No significant changes in sGaw were seen in normal subjects or asthmatic patients following the inhalation of dopamine. Dopamine aerosol produced no symptoms in any of the subjects studied.

The effect of inhaled dopamine on Raw and Vtg is tabulated in Appendix D, Table LV.

DISCUSSION

The present results indicate that dopamine infusion at a dose that has been reported to increase cardiac contractility (Whitsett & Goldberg, 1972), cardiac output and renal blood flow (McDonald et al, 1964), does not significantly alter airflow resistance in normal subjects or in patients with extrinsic asthma. In addition, inhaled dopamine failed to effect airflow resistance in a similar group of subjects. This lack of response in airflow resistance suggests that specific dopamine receptors are unlikely to exist in human airways, and is in keeping with the extremely weak peripheral β -adrenergic agonist action of dopamine found in experimental animals (McNay & Goldberg, 1966).

It is possible, however, that specific dopamine receptors remained unstimulated by the dose of dopamine infused. It was felt unethical to give higher doses of infused dopamine, and this may therefore have limited the access of the drug to receptor sites in the lung. Although it is not possible to accurately estimate the dose of dopamine inhaled it is less likely, by this means of administration, that any lack of response was due to poor access to receptor sites on the airways. If dopamine is released from human mast cells, as has been suggested to occur in bovine lung (Eyre & Deline, 1971), it is unlikely to be a clinically significant factor in the production of airways obstruction.

In doses above 30 mg $Kg^{-1}min^{-1}$ the predominant effect of infused dopamine in all vascular beds examined is vasoconstriction due to its action on α -adrenergic receptors (Goldberg, 1972). α -adrenergic responses have been reported in the airways of both normal subjects (Anthracite et al, 1971; Bianco et al, 1972) and asthmatic patients (Patel & Kerr, 1973; Snashall et al, 1978). However, the dose of dopamine infused in this study was low and, therefore, its effect on dopamine receptors is unlikely to have been masked by any α -adrenergic activity. This was confirmed in six asthmatic patients by the lack of airways response to dopamine when it was infused in combination with the α -adrenergic antagonist thymoxamine.

It is concluded that dopamine has no acute effect

on airflow resistance in man and that specific dopamine receptors are unlikely to exist in human airways.

TABLE X Effect of infused dopamine on sGaw in normal subjects (N = 6) and asthmatic patients (N = 8)

Group			Pre-infusion baseline	Infusion baseline	sGaw(s^{-1} k Pa^{-1}) Time after dopamine infusion (min) 1	3	5	10	15	20
Normals										
	Age	Sex								
D.A.	22	M	1.46		1.45	1.79	1.70	1.27	1.24	1.47
M.D.	36	M	1.18		1.37	1.17	1.16	1.40	1.37	1.33
D.I.	26	M	0.86		1.14	1.05	0.95	0.89	0.94	1.05
K.S.	22	M	1.19		1.58	1.46	1.33	1.30	1.63	1.32
T.H.	22	M	1.44		1.47	1.35	1.16	1.05	1.44	1.09
K.P.	36	M	2.61		2.59	2.68	2.83	2.44	2.19	2.51
Mean			1.45		1.60	1.58	1.52	1.39	1.47	1.46
SEM			0.24		0.21	0.24	0.28	0.22	0.17	0.21
P value					NS	NS	NS	NS	NS	NS
Asthmatics										
Study No										
1			0.95	0.81	0.68		0.71	0.79		0.78
2			0.55	0.42	0.47		0.43	0.52		0.60
3			0.64	0.55	0.62		0.56	0.63		0.55
4			0.71	0.73	0.65		0.69	0.65		0.66
5			0.66	0.63	0.70		0.76	0.72		0.71
6			0.41	0.36	0.33		0.38	0.28		0.30
7			0.93	0.64	0.58		0.42	0.39		0.33
8			0.80	1.07	0.85		0.75	0.85		0.80
Mean			0.71	0.65	0.61		0.59	0.60		0.59
SEM			0.06	0.05	0.05		0.05	0.06		0.06
P value					NS		NS	NS		NS

Infusion baseline refers to values after dextrose (50 g/l) infusion without dopamine

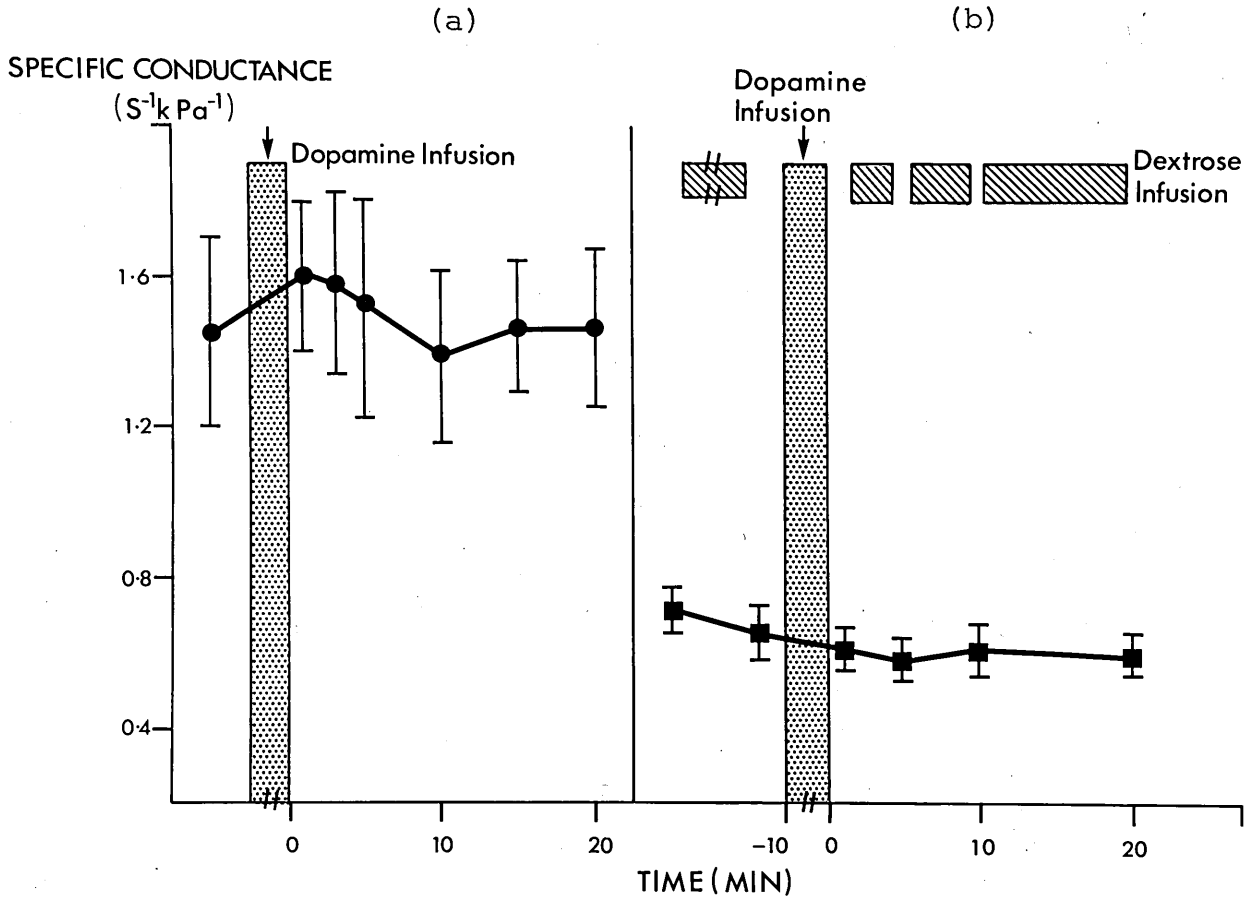

FIGURE 12 EFFECT OF INFUSED DOPAMINE ON sGaw IN (a) NORMAL SUBJECTS (N = 6) AND (b) ASTHMATIC PATIENTS (N = 8)

TABLE XI Effect of infused thymoxamine alone and in combination with dopamine on sGaw in asthmatic patients (N = 6)

Study No	Baseline	Thymoxamine alone	Change after thymoxamine plus dopamine 1 min	5 min
3	0.55	0.60	0.64	0.67
4	0.66	0.65	0.74	0.56
5	0.71	0.73	0.72	0.75
6	0.30	0.37	0.40	0.36
7	0.33	0.31	0.42	0.53
8	0.64	0.74	0.62	0.65
Mean	0.53	0.57	0.59	0.59
SEM	0.07	0.07	0.06	0.05
P value			NS	NS

sGaw (s^{-1} k Pa^{-1})

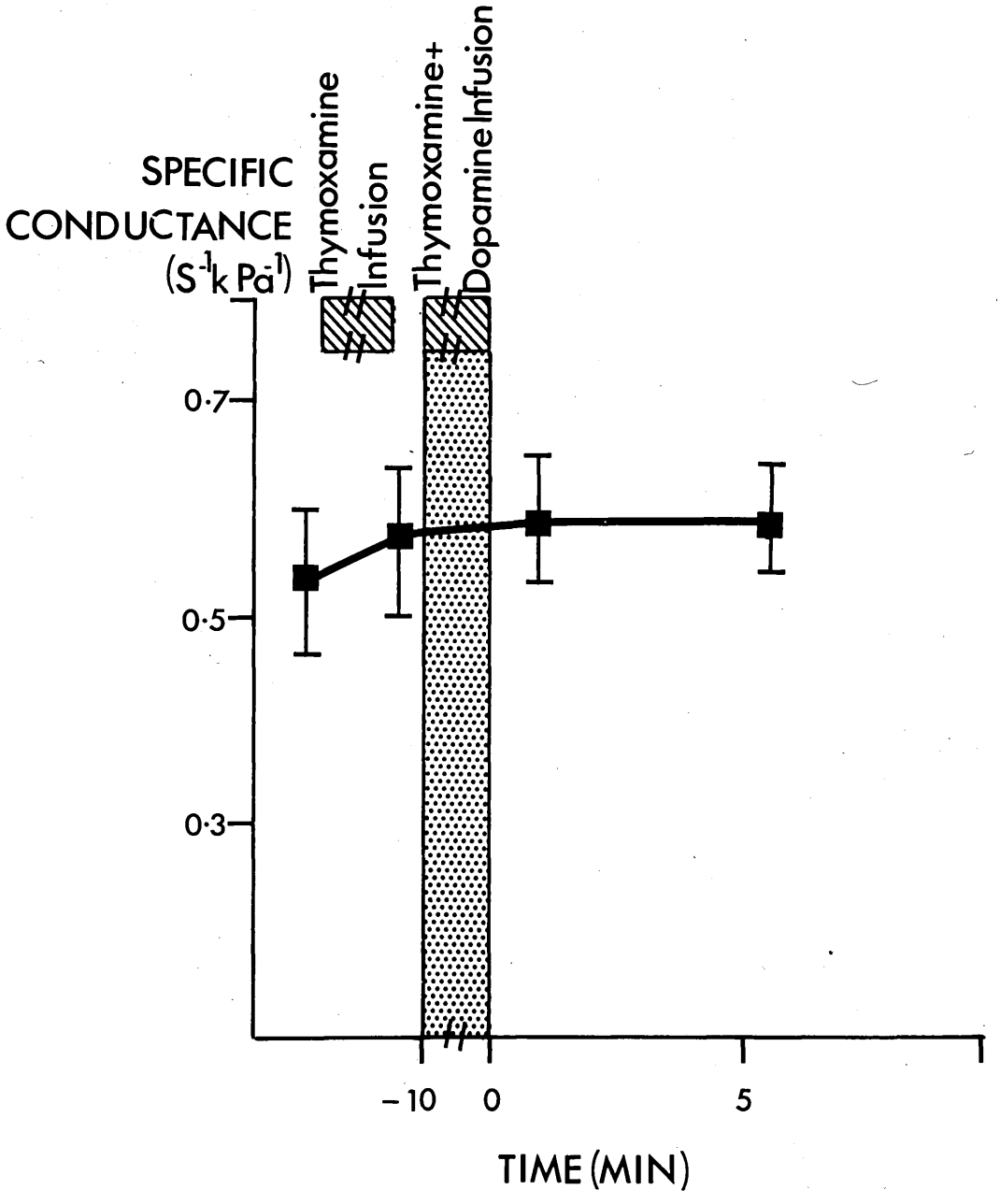

FIGURE 13 EFFECT OF INFUSED THYMOXAMINE ALONE AND IN COMBINATION WITH DOPAMINE ON sGaw IN ASTHMATIC PATIENTS (N = 6)

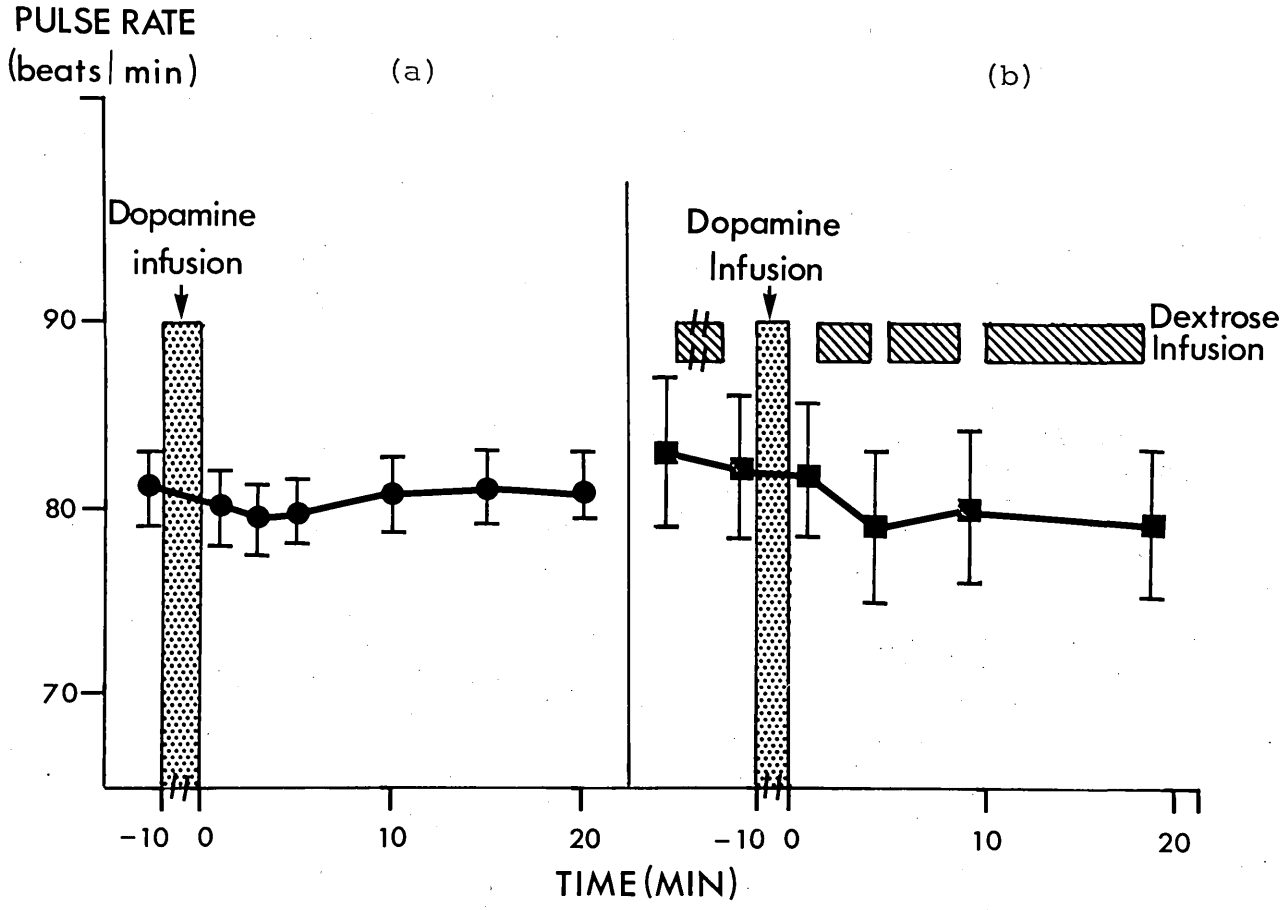

FIGURE 14 EFFECT OF INFUSED DOPAMINE ON RADIAL PULSE RATE IN (a) NORMAL SUBJECTS (N = 6) AND (b) ASTHMATIC PATIENTS (N = 8)

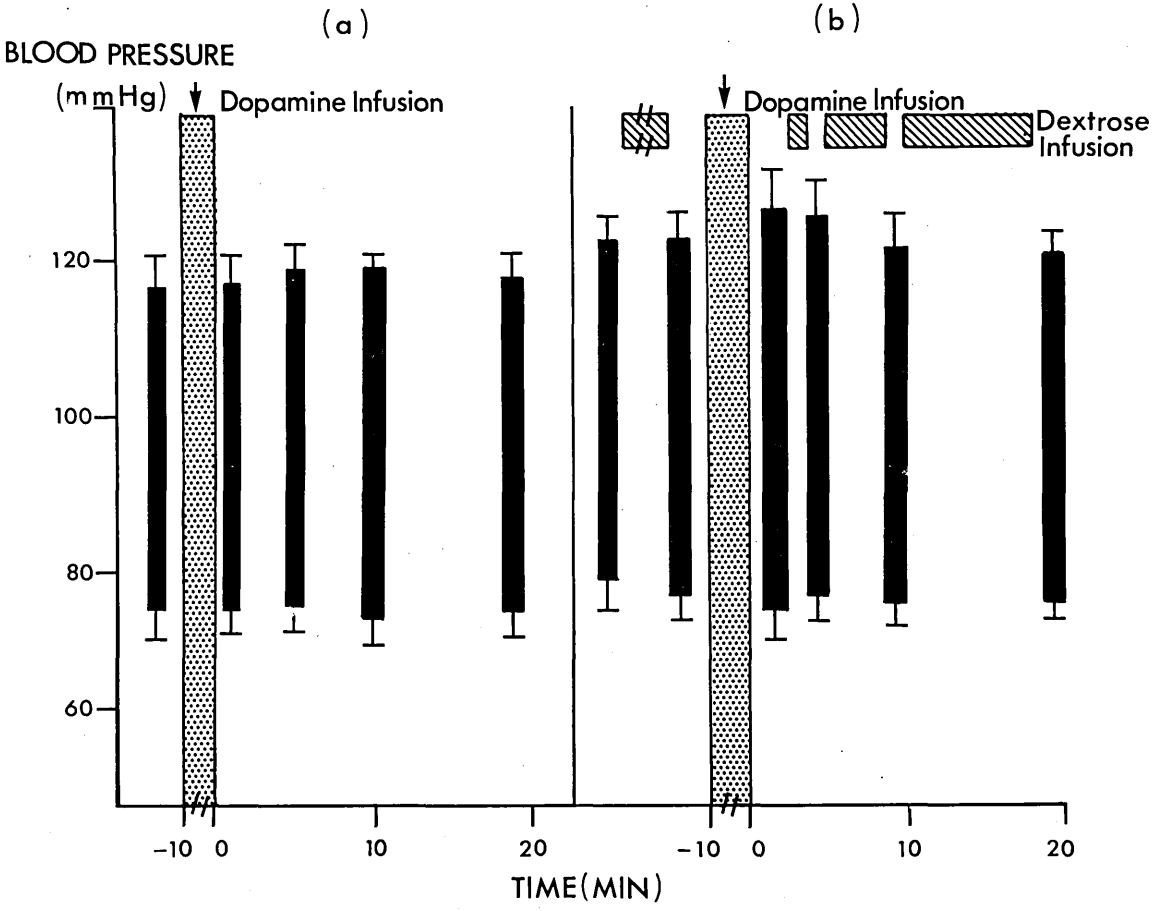

FIGURE 15 EFFECT OF INFUSED DOPAMINE ON BLOOD PRESSURE IN (a) NORMAL SUBJECTS (N = 6) AND (b) ASTHMATIC PATIENTS (N = 8)

TABLE XII Effect of inhaled dopamine on sGaw in normal subjects (N = 6) and asthmatic patients (N = 6)

Group			Baseline	Post-saline	sGaw (s^{-1} k Pa^{-1}) Dose of dopamine (g/l) 0.5	1.0	2.0
Normals							
	Age	Sex					
K.P.	36	M	3.45	3.72	3.68	3.41	3.57
D.A.	22	M	2.37	2.47	2.01	2.08	2.26
A.C.	26	M	2.02	1.81	1.83	1.78	1.81
D.I.	26	M	1.13	1.08	1.15	1.21	1.20
B.R.	27	M	1.58	1.53	1.49	1.57	1.54
B.McD.	24	M	3.30	3.10	3.02	2.98	2.99
Mean			2.30	2.28	2.19	2.17	2.22
SEM			0.37	0.40	0.39	0.34	0.36
P value					NS	NS	NS
Asthmatics							
Study No							
2			0.78	0.63	0.59	0.67	0.57
7			0.50	0.50	0.56	0.49	0.57
9			1.20	1.01	0.95	1.07	0.98
10			0.44	0.34	0.34	0.38	0.36
11			0.40	0.32	0.28	0.29	0.29
12			1.55	1.45	1.27	1.94	1.26
Mean			0.97	0.71	0.67	0.81	0.67
SEM			0.12	0.18	0.15	0.25	0.15
P value					NS	NS	NS

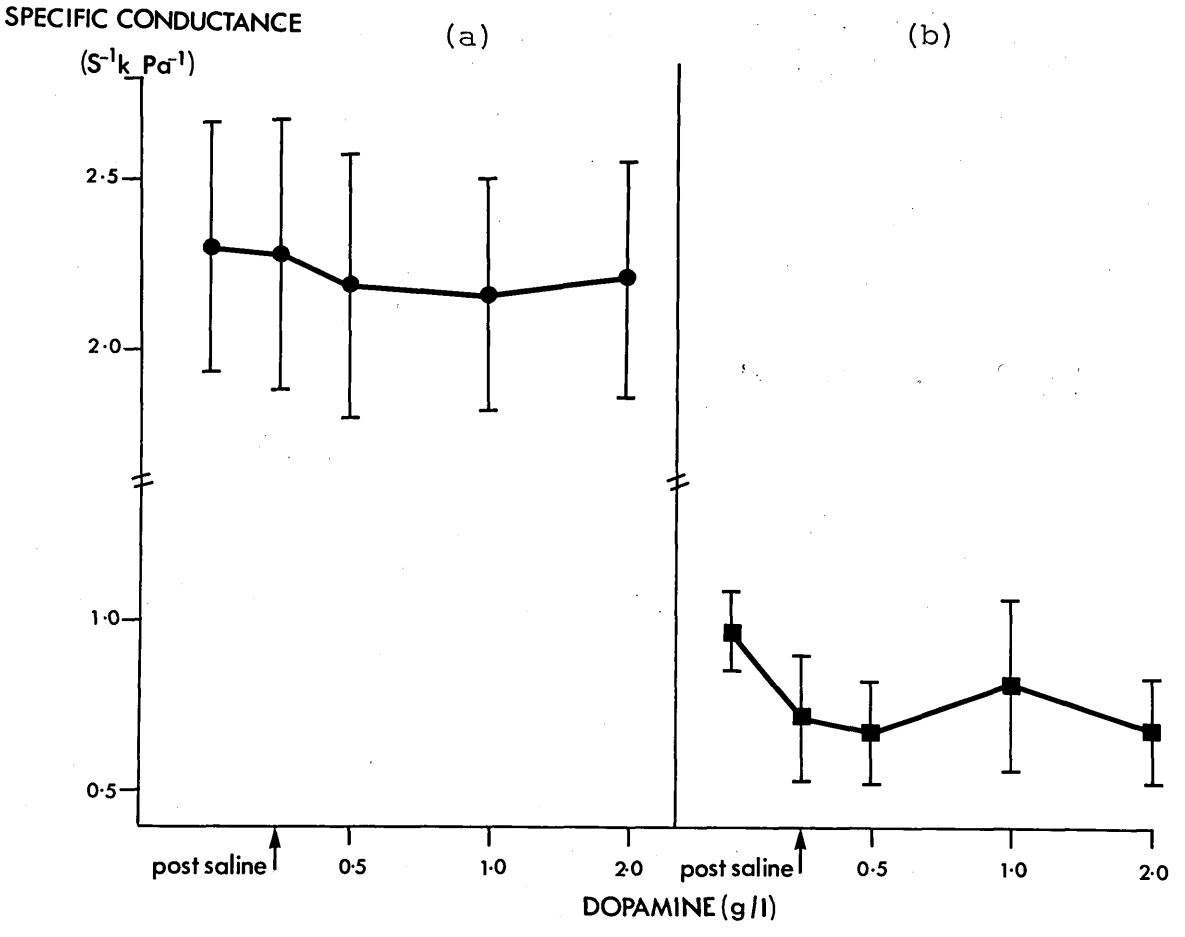

FIGURE 16 EFFECT OF INHALED DOPAMINE ON sGaw IN (a) NORMAL SUBJECTS (N = 6) AND (b) ASTHMATIC PATIENTS (N = 6)

CHAPTER V

EFFECT OF AFFERENT AND EFFERENT VAGAL BLOCKADE ON EXPERIMENTAL BRONCHOCONSTRICTION

INTRODUCTION

In experimental animals it has been postulated that allergen-induced bronchoconstriction is due to stimulation of irritant receptors in the bronchial epithelium, which elicit reflex vagal bronchoconstriction, and that a similar mechanism may occur in human asthma (Gold, 1975; Widdicombe, 1977). Circumstantial evidence for reflex bronchoconstriction in human asthma is based on blocking efferent vagal motor actions by anticholinergic drugs (Yu *et al*, 1972; Empey *et al*, 1976). Local anaesthetics have been used to inhibit afferent vagal sensory endings in animals (Jain *et al*, 1973; Dain *et al*, 1975). In patients with asthma, Petit & Delhez (1970) studied the effect of inhaled lignocaine combined with ephedrine, although the inclusion of ephedrine makes interpretation of their results difficult. More recently, Cross *et al* (1976) demonstrated that an aerosol of bupivacaine hydrochloride can produce reversible anaesthesia of the airways in man, which inhibited the cough reflex, and abolished the afferent pathway of a reflex induced bronchoconstriction in one normal subject.

The purpose of this study was to investigate the effects of afferent and efferent vagal blockade on experimental bronchoconstriction in normal subjects and in patients with extrinsic asthma.

METHODS

Eight patients with extrinsic asthma (Table XIII) and fourteen normal subjects (seven smoked 10 - 15

TABLE XIII Clinical details of asthmatic patients

Patient No	Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean Baseline FEV_1 (l)	% Predicted FEV_1
1 S.McK.	17	M	160	63	2.95	82.8
2 M.S.	34	M	165	70	3.25	91.5
3 J.C.	21	M	165	69	3.69	97.1
4 G.B.	23	M	167	69	4.10	105.1
5 B.McL.	18	M	168	68	3.91	100.2
6 E.T.	31	F	169	75	2.91	88.1
7 V.D.	25	F	159	62	3.05	101.6
8 R.S.	24	M	175	81	3.71	90.4

cigarettes per day) were studied. FEV_1 was measured in triplicate on a dry wedge spirometer (Vitalograph) at the start of each study day, the best recording being used for analysis. The mean of six recordings was calculated to give sGaw. In each subject, tests were performed at the same time of day.

Powdered bupivacaine hydrochloride was dissolved in water to make a 4% solution (116.6 mmol/l). This solution was inhaled through a Wright nebuliser for two 6 min periods separated by 1 min. The full 12 min of aerosol administration was performed during normal tidal breathing (a deep inspiration to total lung capacity was also taken every 30 sec in the experiments involving the inhalation of cigarette smoke). Bupivacaine aerosol was generated at room temperature and the estimated dose nebulised was 100 mg (291.5 μmol/l). Experiments were performed within 10 min of inhaling bupivacaine aerosol. Ipratropium bromide (1 g/l, 2.4 mmol/l) and sodium cromoglycate (10 g/l, 19.5 mmol/l) were also administered via a Wright nebuliser for 12 min. The estimated dose of ipratropium bromide nebulised was 2.0 mg (4.8 μmol), and that of sodium cromoglycate 20 mg (39.0 μmol). Studies were carried out 30 min after inhaling ipratropium bromide and sodium cromoglycate. Control aerosols of sodium chloride (9 g/l, 0.15 mol/l) were administered in exactly the same manner as the active drugs. Pre-treatments were randomly assigned.

Experimental Procedures

Cough reflex. This was tested in six normal and four asthmatic patients using a solution of citric acid at concentrations of 200 g/l and 100 g/l respectively from a Wright nebuliser, with a control solution of saline, the subject being unaware of which solution was to be administered. A cough was recorded as being either present or absent after one to a maximum of five normal inspirations as described by Bickerman & Barach (1954). The cough reflex was tested in both normal subjects and asthmatics after the administration of either bupivacaine, sodium cromoglycate or saline.

Bronchial response to bupivacaine. In five normal subjects following baseline measurements of sGaw before and after saline, bupivacaine or saline was inhaled through a Wright nebuliser for two 6 min periods separated by 1 min, sGaw then being recorded at 1, 5, 10, 15 and 20 min. A similar protocol was used in five asthmatics, except that bupivacaine was nebulised for only 6 min and ipratropium bromide was inhaled prior to bupivacaine.

Bronchial response to methacholine. In five normal subjects following baseline measurements of sGaw, methacholine dihydrochloride (10 g/l, 51.0 mmol/l) was inhaled through a Wright nebuliser for 2 min, with sGaw then recorded at 1, 5 and 10 min. Bupivacaine, ipratropium bromide or saline was inhaled separately prior to methacholine. In six asthmatics ipratropium

bromide or saline was each administered separately prior to methacholine (1 g/l, 5.1 mmol/l).

Bronchial response to histamine. Histamine dihydrochloride (5 g/l, 27.1 mmol/l) and (2 g/l, 10.8 mmol/l) was given in a similar manner to methacholine to six normal subjects, three of whom had an upper respiratory tract infection. Bupivacaine, ipratropium bromide, sodium cromoglycate or saline was each given separately prior to histamine (5 g/l, 27.1 mmol/l).

Bronchial response to prostaglandin $F_2\alpha$. Prostaglandin (PG) $F_2\alpha$ (0.5 g/l, 1.0 mmol/l) was administered in a similar manner to methacholine and histamine to five normal subjects following either bupivacaine, ipratropium bromide or saline. sGaw was recorded at 1 and 5 min.

Bronchial response to cigarette smoke. In eight normal subjects (seven of whom were regular smokers) following baseline measurements of sGaw, cigarette smoke was inhaled every 30 sec for 5 min from a medium tar filter-tipped cigarette, with sGaw then recorded at 2 min. Bupivacaine, ipratropium bromide, sodium cromoglycate or saline was each administered separately prior to the inhalation of cigarette smoke. All subjects abstained from smoking for a minimum of 2 hr prior to testing.

Statistical comparisons were made by the Fisher, Irwin & Yates exact probability test and Wilcoxon match-pairs signed-rank test (experiment involving eight subjects only). Differences were considered significant if $P < 0.05$.

RESULTS

Cough reflex (Table XIV)

An aerosol of citric acid (200 g/l) produced a cough in six normal subjects after one to four inhalations. No cough reflex was produced after saline aerosol. Bupivacaine aerosol prevented the cough reflex in all subjects, even with five inhalations of citric acid. Sodium cromoglycate had no preventive action on the cough reflex, and in each subject the number of inhalations of citric acid required to produce cough was identical to the control experiment.

In asthmatic patients a cough reflex was elicited after one to four inhalations of an aerosol of citric acid (100 g/l). Although bupivacaine produced bronchoconstriction it prevented the cough reflex even with five inhalations, whereas sodium cromoglycate had no preventive action. In both normal subjects and asthmatics the cough produced by citric acid was accompanied by a slight raw sensation in the throat and anterior upper chest. This sensation was only prevented by pre-treatment with bupivacaine.

Bronchial response to bupivacaine

All subjects noted that bupivacaine aerosol tasted bitter particularly during the first few min of inhalation and was associated with a cough in some subjects. Bupivacaine had no significant effect on

sGaw in normal subjects (Table XV) but produced a significant bronchoconstriction at 1, 5, 10 and 20 min in the asthmatic patients (Table XVI, Figure 17). This fall in sGaw was significantly reduced ($P < 0.05$) by pre-treatment with ipratropium bromide.

Bronchial response to methacholine (Tables XVII, XVIII; Figure 18)

Methacholine aerosol produced slight throat irritation associated with an occasional cough in normal subjects. These sensations were abolished by pre-treatment with bupivacaine. Ipratropium bromide significantly prevented the fall in sGaw due to methacholine ($P < 0.05$) whereas bupivacaine had no protective effect. In six asthmatic patients, ipratropium bromide prevented the changes in sGaw due to methacholine.

Bronchial response to histamine (Table XIX, Figure 19)

Histamine aerosol produced slight throat irritation, occasional cough and mild retrosternal tightness in most normal subjects. The change in sGaw due to histamine was partially reduced by ipratropium bromide at 1 min, but not at 5 or 10 min, while bupivacaine and sodium cromoglycate had no preventive effect. Bupivacaine abolished the sensations associated with histamine inhalation. The three subjects who had an upper respiratory tract infection showed similar changes in sGaw due to histamine as the other normal subjects. The effect of pre-treatment with ipratropium

bromide, bupivacaine or sodium cromoglycate on histamine induced bronchoconstriction did not differ between the two groups.

Bronchial response to prostaglandin $F_{2\alpha}$ (Table XX, Figure 20)

Normal subjects experienced initial coughing, retrosternal tightness and produced small amounts of watery sputum. Bupivacaine prevented the initial cough and retrosternal tightness, but had no effect on the watery sputum, which was prevented by ipratropium bromide. Neither ipratropium bromide or bupivacaine prevented the changes in sGaw in the normal subjects.

Bronchial response to cigarette smoke (Table XXI, Figure 21)

Ipratropium bromide significantly prevented the fall in sGaw due to cigarette smoke ($P < 0.05$), whereas bupivacaine or sodium cromoglycate had no protective effect.

The effects of the above agents on Raw and Vtg are tabulated in Appendix D, Tables LVI - LXIV.

DISCUSSION

In experimental animals cough receptors are concentrated especially in the larynx and tracheal bifurcation, whereas irritant receptors are found within the lung to the level of the bronchioles (Fillenz & Widdicombe, 1972). The more proximal

cough receptors are, therefore, likely to be exposed to greater quantities of aerosol than the more distal irritant receptors. In the present study a 4% bupivacaine solution was given for 12 min at room temperature without any significant side effects in normal subjects. The total dose of bupivacaine delivered to the airways by this method was similar to that of Cross et al, (1976) who used a heated aerosol of bupivacaine. Although bupivacaine aerosol administered by the method described here could abolish the cough reflex in both normal and asthmatic patients, it is unknown whether complete irritant receptor blockade was achieved. The inhalation technique used to give pharmacological blocking and bronchoconstricting aerosols was, however, the same, so that in any one subject the deposition of aerosols within the airways should have been similar, even if the sites of action were different. In addition, the pharmacological blocking drugs were inhaled for six times the duration of the bronchoconstricting agents.

Bupivacaine aerosol had no effect on airways conductance in normal subjects, as reported by Cross et al, (1976), who found that two patients with bronchial asthma developed severe asthma after bupivacaine aerosol. The present results extend this observation in asthmatics and so confirm the bronchoconstriction effect of bupivacaine. This precluded its use for further study with other bronchoconstrictor agents in asthmatic patients. The

reason for the bronchial hyper-reactivity to bupivacaine and the partial reduction of this by ipratropium bromide is unknown. Although the inhalation of irritant aerosols may increase laryngeal resistance (Stransky, Szereda-Przestaszewaka & Widdicombe, 1973; Szereda-Przestaszewaka, 1974), this is unlikely to have altered sGaw when measured, as in this study, at a flow rate of 0.5 l/s with the larynx held open. Furthermore, laryngeal resistance would be resistant to an anticholinergic drug, since the intrinsic laryngeal muscles are striated. The inhibitory action of ipratropium bromide, at a dose sufficient to prevent methacholine induced bronchoconstriction, suggests that bupivacaine might be partially acting via a vagal pathway. Alternatively, the bronchodilation from ipratropium bromide might result in reduced bronchial reactivity, due to a change in baseline airflow obstruction (Benson, 1975), although the difference between baseline values after saline or ipratropium bromide was small. The sites of action of bupivacaine on the airways appears to be on the afferent vagal receptors (Jain et al, 1973; Dain et al, 1975) and probably also on the post ganglionic parasympathetic motor fibres in the muscular layer of the airway wall (Dain et al, 1975). Methacholine acts on the smooth muscle cholinergic receptor, and probably has no direct effect on irritant receptors (Vidruk et al, 1977). It seems likely, therefore, that bupivacaine has no blocking action on the smooth muscle cholinergic

receptors, since in normal subjects the bronchial response to methacholine was prevented by ipratropium bromide but not by bupivacaine.

Sodium cromoglycate is thought to act by temporarily stabilising the mast cell and so preventing mediator release (Orr et al, 1970). More recently, using a canine model of reflex bronchoconstriction, Jackson & Richards (1977) suggested that sodium cromoglycate may also reduce the activity of lung irritant receptors, and by this means reduce asthmatic attacks in man. In the present study, however, sodium cromoglycate given at the normal therapeutic dose of 20 mg did not inhibit the cough reflex in either normal subjects or asthmatic patients. The bronchoconstrictor effects of cigarette smoke and histamine, which have been postulated to have reflex vagal actions (Nadel & Comroe, 1961; Empey et al, 1976) were also not inhibited by sodium cromoglycate in normal subjects. In addition, sodium cromoglycate has been shown to be ineffective in preventing the bronchoconstrictor response to histamine (Kang et al, 1976; Cockcroft et al, 1977[b]) in asthmatics.

If the dose and method of administration of bupivacaine was sufficient to block irritant receptors, then the present results indicate that histamine was not acting on these receptors. The partial inhibition of histamine-induced bronchoconstriction by an anticholinergic drug does, however, suggest that vagal

pathways may be involved. Alternatively, ipratropium bromide could have left the airway smooth muscle fully relaxed and less responsive to constrictor influences, although the mean baseline value of sGaw after ipratropium bromide or bupivacaine was similar. Upper respiratory tract infections in healthy human subjects produces transient bronchial hyper-reactivity to inhaled histamine, which can be inhibited by atropine (Empey et al,1976). These authors suggested that vagal sensory receptors are sensitized by viral respiratory infection which when stimulated by histamine produce reflex vagal bronchoconstriction. The vagal component of this bronchial hyper-reactivity to histamine may, however, comprise predominantly efferent vagal hypersensitivity. In support of this, increased response to methacholine has been reported in normal subjects with an acute respiratory tract infection (Parker et al, 1965). The effect of histamine on normal airways is only partially prevented by ipratropium bromide, suggesting that the main site of action of histamine is probably directly on bronchial smooth muscle via H_1 receptors (Chapter III).

There is a marked and unexplained difference in the sensitivity of asthmatic and normal subjects to inhaled $PGF_2\alpha$ (Mathé et al, 1973). The failure of ipratropium bromide or bupivacaine to significantly prevent $PGF_2\alpha$ induced bronchoconstriction in normal subjects is in agreement with previous reports using atropine (Mathé & Hedqvist, 1975; Smith, Cuthbert & Dunlop, 1975; Newball

& Lenfant, 1977), and indicates that $PGF_2\alpha$ is probably acting directly on bronchial smooth muscle rather than by vagal pathways.

Reflex vagal bronchoconstriction secondary to stimulation of irritant receptors by inhaled cigarette smoke occurs in rabbits (Sellick & Widdicombe, 1971), but only to a minor degree in dogs (Sampson & Vidruk, 1975). It has been suggested that cigarette smoke may act on irritant receptors in humans (Nadel & Comroe, 1961) and this is supported by the finding that anticholinergic drugs block this response (Sterling, 1967; Gayrard, Orehek & Charpin, 1975). Despite the marked variability of bronchial responses to smoking (Clarke et al, 1970) the present results suggest that inhaled cigarette smoke was not acting on these receptors. Since cigarette smoke acts predominately on the larger central airways (DaSilva & Hamosh, 1973; Costello et al, 1975) it is unlikely that insufficient irritant receptor blockade by bupivacaine could explain these findings. The reason for the bronchial reactivity to cigarette smoke in normal subjects remains unexplained, but both the particulate and vapour phase of smoke appear to be involved (Clarke et al, 1970).

Increased irritant receptor sensitivity has been postulated to be the cause of the exaggerated airway reactivity characteristic of asthma (Nadel, 1977; Widdicombe, 1977). Experimental support for this in man has been based mainly on blocking efferent vagal motor actions of anticholinergic drugs. However, in

normal subjects the present results suggest that a reduction in bronchoconstrictor response following an anticholinergic drug may not necessarily indicate a reflex vagal pathway. Unfortunately, the bronchoconstricting action of bupivacaine precluded its use in further defining the vagal component of bronchial hyper-reactivity in asthmatic patients.

TABLE XIV Effect of inhaled citric acid on the cough reflex in normal subjects (N = 6) and asthmatic patients (N = 4)

Group			Breaths of inhaled citric acid to produce cough*		
			Saline pre-treatment	Bupivacaine pre-treatment	Sodium cromoglycate pre-treatment
Normals	Age	Sex			
A.McF.	23	F	1	>5	1
R.G.	22	F	4	>5	4
D.I.	26	M	1	>5	1
N.T.	30	M	4	>5	4
I.W.	36	M	1	>5	1
K.P.	36	M	2	>5	2
Asthmatics					
Study No					
2			1	>5	2
3			4	>5	4
1			3	>5	4
4			2	>5	2

* Mean of two measurements

TABLE XV Effect of inhaled bupivacaine and saline on sGaw in normal subjects (N = 5)

Subject	Age	Sex	Baseline sGaw ($s^{-1}k\ Pa^{-1}$)	Change in sGaw after inhalation				
				1 min	5 min	10 min	15 min	20 min
						Saline		
I.W.	36	M	1.50	+0.03	+0.09	+0.06	+0.07	+0.03
R.G.	22	F	2.10	-0.09	-0.07	-0.11	-0.13	-0.20
D.I.	26	M	0.90	-0.02	-0.03	+0.00	+0.02	+0.01
K.C.	25	M	0.97	-0.02	+0.02	-0.02	-0.03	-0.01
K.P.	36	M	4.00	+0.20	-0.08	-0.05	-0.09	-0.09
Mean			1.89	+0.02	-0.01	-0.02	+0.06	-0.05
SEM			0.56	0.04	0.03	0.02	0.02	0.04
						Bupivacaine		
I.W.	36	M	1.42	+0.20	+0.13	+0.06	-0.04	-0.05
R.G.	22	F	2.40	+0.08	-0.05	-0.02	-0.02	+0.00
D.I.	26	M	0.87	+0.03	-0.04	-0.03	-0.04	-0.01
K.C.	25	M	0.97	-0.01	+0.00	-0.02	-0.02	-0.01
K.P.	36	M	4.22	-0.30	-0.35	-0.28	-0.30	-0.28
Mean			1.97	-0.08	-0.16	-0.09	-0.07	-0.05
SEM			0.62	0.15	0.17	0.08	0.05	0.05

* Values significantly different from those with saline pre-treatment at that time ($p < 0.05$)

TABLE XVI Effect of inhaled bupivacaine and saline on sGaw in asthmatic patients (N = 5)

Patient No	Pre-treatment	Baseline sGaw ($s^{-1}kPa^{-1}$)		Change in sGaw after bupivacaine				
		B	A	1 min	5 min	10 min	15 min	20 min
1	Saline	0.73	0.79	-0.58	-0.58	-0.55	-0.54	-0.50
2		0.45	0.46	-0.27	-0.27	-0.30	-0.30	-0.30
3		1.09	1.08	-0.34	-0.30	-0.31	-0.32	-0.29
4		2.03	2.11	-0.29	-0.78	-0.91	-0.79	-0.58
5		0.79	0.84	-0.50	-0.59	-0.58	-0.56	-0.58
Mean		1.01	1.06	-0.40	-0.50	-0.53	-0.50	-0.45
SEM		0.32	0.28	0.06	0.09	0.11	0.09	0.06
1	Ipratropium	0.73	1.16	-0.12	-0.27	-0.29	-0.30	-0.28
2		0.55	0.98	-0.04	-0.08	-0.13	-0.05	-0.03
3		0.88	0.91	-0.09	-0.20	-0.26	-0.35	-0.27
4		1.53	2.85	+0.22	+0.52	+0.11	+0.12	+0.03
5		0.56	0.91	-0.06	-0.16	-0.18	-0.18	-0.15
Mean		0.85	1.36	-0.02*	-0.04*	-0.15*	-0.15*	-0.14*
SEM		0.18	0.37	0.06	0.14	0.07	0.08	0.06

B, before pre-treatment; A, after saline or ipratropium

* Values significantly different from those with saline pre-treatment at that time ($p < 0.05$)

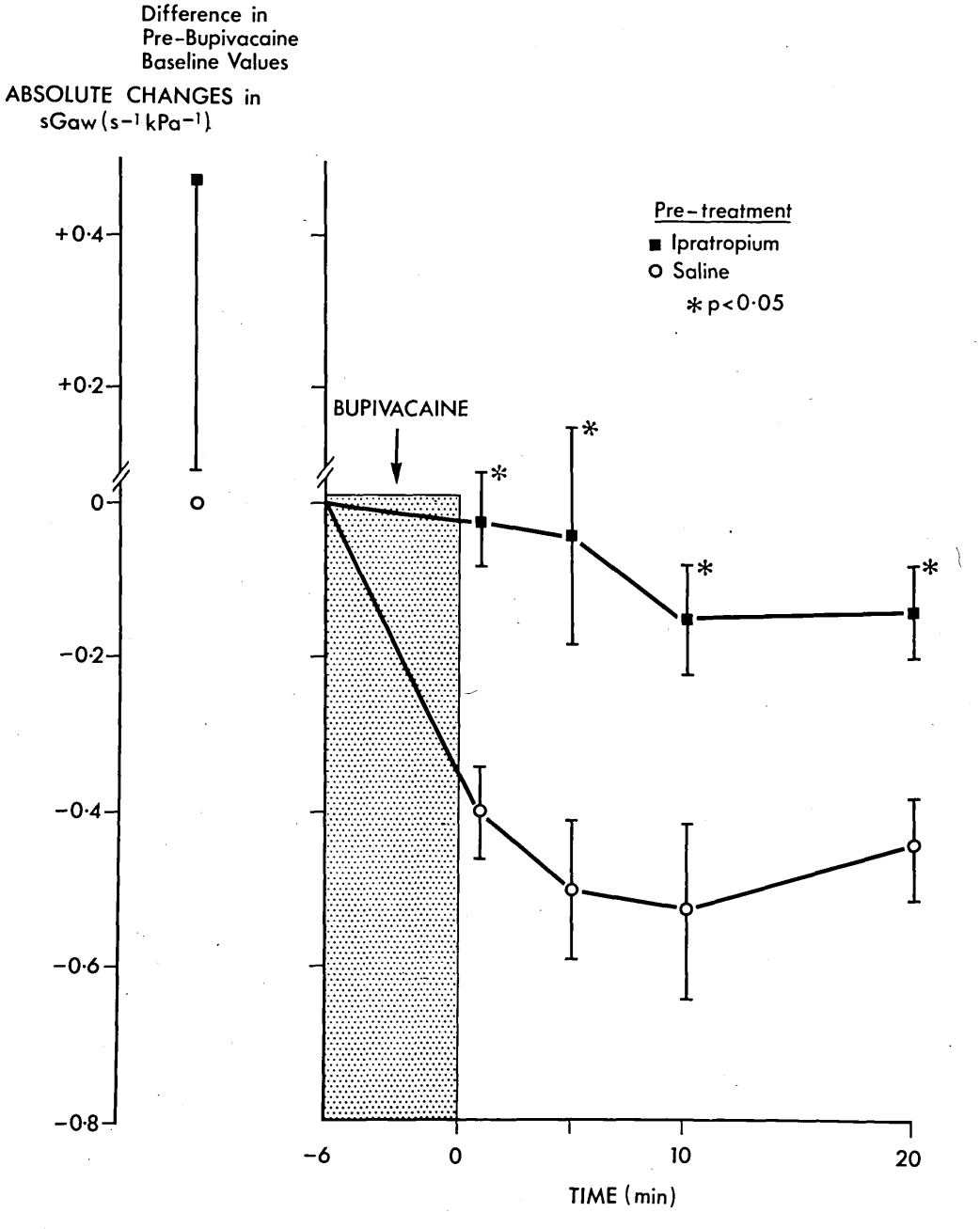

FIGURE 17 EFFECT OF INHALED BUPIVACAINE ON sGAW IN ASTHMATIC PATIENTS (N = 5)

TABLE XVII Effect of inhaled methacholine on sGaw following ipratropium, bupivacaine or saline in normal subjects (N=5)

Subject	Pre-treatment	Baseline sGaw ($s^{-1}kPa^{-1}$)		Change in sGaw after methacholine (10 g/l)		
		B	A	1 min	5 min	10 min
I.W.	Saline	1.32	1.27	-0.48	-0.39	-0.55
K.C.		1.35	1.37	-0.78	-0.80	-0.86
R.G.		2.19	2.08	-1.30	-1.32	-1.19
R.S.		1.78	1.64	-1.11	-0.95	-0.93
D.I.		0.76	0.68	-0.53	-0.42	-0.41
Mean		1.48	1.40	-0.84	-0.78	-0.79
SEM		0.23	0.22	0.16	0.17	0.14
I.W.	Ipratropium	1.35	1.46	+0.37	+0.15	+0.25
K.C.		1.32	1.66	+0.05	+0.02	+0.06
R.G.		2.69	4.07	+0.25	+0.34	+0.27
R.S.		1.50	2.21	+0.20	+0.19	+0.16
D.I.		0.71	0.90	+0.02	-0.12	+0.00
Mean		1.51	2.06	+0.18*	+0.12*	+0.15*
SEM		0.31	0.54	0.06	0.08	0.05
I.W.	Bupivacaine	1.03	1.21	-0.42	-0.52	-0.55
K.C.		1.22	1.16	-0.31	-0.46	-0.41
R.G.		2.50	2.42	-1.49	-1.13	-1.05
R.S.		1.51	1.41	-0.74	-0.58	-0.49
D.I.		0.76	0.68	-0.21	-0.28	-0.28
Mean		1.40	1.37	-0.63	-0.59	-0.56
SEM		0.28	0.28	0.23	0.14	0.13

B, before pre-treatment; A, after saline, ipratropium or bupivacaine

* Values significantly different from those with saline pre-treatment at that time ($p < 0.05$)

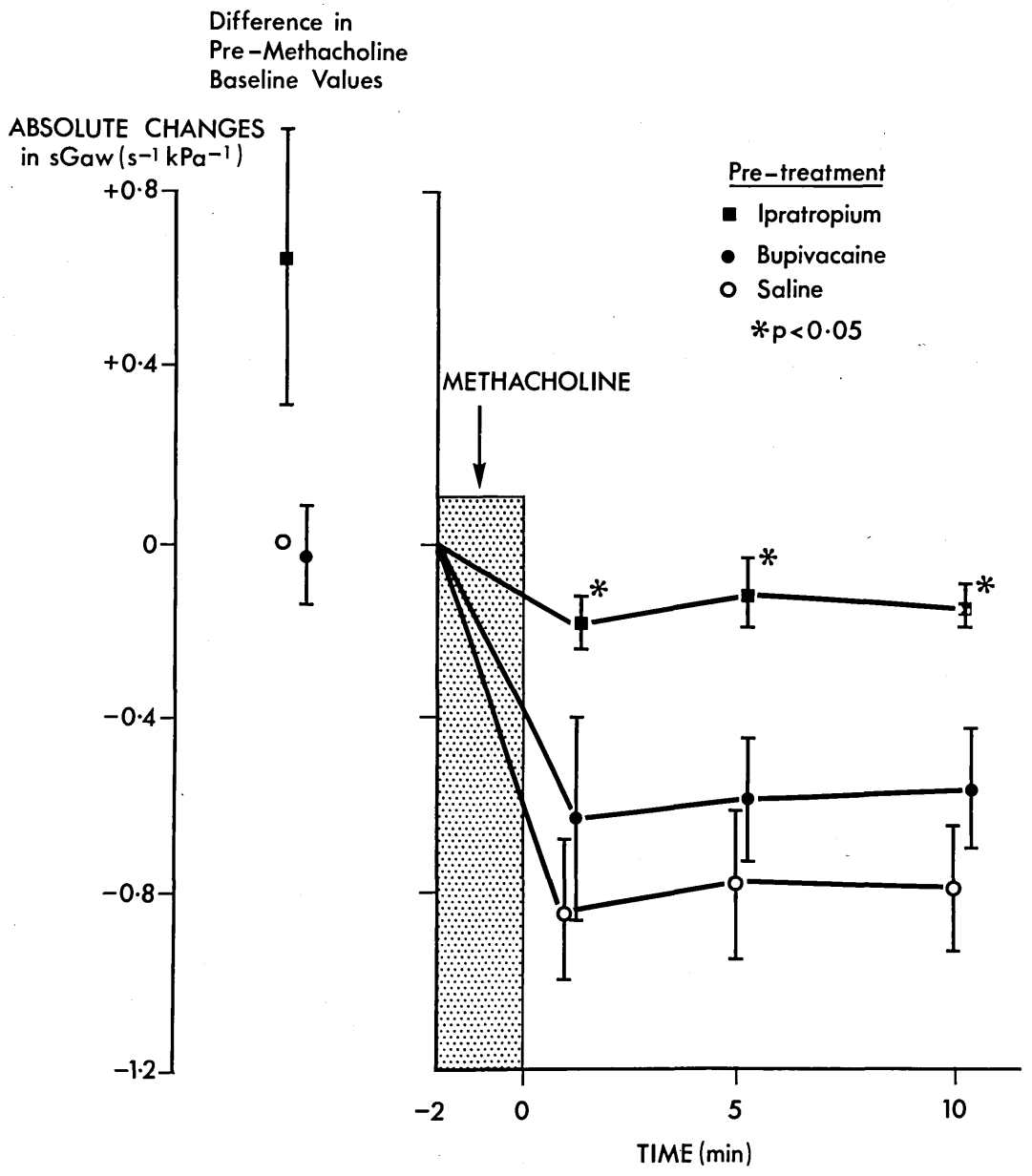

FIGURE 18 EFFECT OF INHALED METHACHOLINE ON sGaw FOLLOWING IPRATROPIUM, BUPIVACAINE OR SALINE IN NORMAL SUBJECTS (N = 5)

TABLE XVIII Effect of inhaled methacholine on sGaw following ipratropium or saline in asthmatic patients (N=6)

Patient No	Pre-treatment	Baseline sGaw ($s^{-1}kPa^{-1}$)		Change in sGaw after methacholine (1 g/l)		
		B	A	1 min	5 min	10 min
1	Saline	0.66	0.66	-0.51	-0.49	-0.47
2		0.71	0.75	-0.55	-0.50	-0.46
3		0.43	0.41	-0.31	-0.31	-0.31
4		1.43	1.53	-1.11	-1.08	-0.95
5		0.89	0.84	-0.61	-0.31	-0.17
6		1.38	1.36	-0.83	-0.66	-0.51
Mean		0.91	0.92	-0.65	-0.56	-0.48
SEM		0.17	0.17	0.11	0.12	0.11
1	Ipratropium	0.50	0.78	-0.04	-0.05	-0.02
2		0.56	0.98	+0.01	+0.00	+0.01
3		0.41	0.80	+0.03	+0.01	+0.04
4		1.70	2.30	+0.01	-0.05	-0.01
5		0.72	1.01	-0.03	-0.02	+0.06
6		1.26	1.70	+0.05	+0.10	+0.09
Mean		0.85	1.26	+0.01*	+0.00*	+0.02*
SEM		0.20	0.24	0.01	0.02	0.01

B, before pre-treatment; A, after saline or ipratropium

* Values significantly different from those with saline pre-treatment at that time ($p < 0.05$)

TABLE XIX Effect of inhaled histamine on sGaw following ipratropium, bupivacaine, sodium cromoglycate or saline in normal subjects (N=6)

Subject	Pre-treatment	Baseline sGaw ($s^{-1}kPa^{-1}$) B	Baseline sGaw ($s^{-1}kPa^{-1}$) A	Change in sGaw after histamine (5 g/l) 1 min	5 min	10 min
D.I.	Saline	0.66	0.68	-0.15	-0.20	-0.11
I.W.		1.35	1.21	-0.43	-0.52	-0.37
A.G.		2.45	2.11	-1.20	-0.90	-0.62
K.C. +		1.62	1.58	-0.62	-0.54	-0.46
R.G. +		3.12	2.98	-1.66	-1.82	-1.28
N.T. +		1.29	1.52	-0.40	-0.60	-0.45
Mean		1.74	1.68	-0.74	-0.76	-0.54
SEM		0.36	0.32	0.23	0.23	0.16
D.I.	Ipratropium	0.77	0.96	-0.13	-0.20	-0.11
I.W.		0.94	1.28	-0.10	-0.52	-0.37
A.G.		2.25	3.21	-0.70	-0.89	-1.12
K.C. +		1.44	1.56	-0.04	-0.19	-0.53
R.G. +		2.76	3.73	+0.61	-0.70	-1.08
N.T. +		1.81	2.01	+0.00	-0.03	-0.06
Mean		1.66	2.12	-0.26*	-0.40	-0.57
SEM		0.31	0.45	0.12	0.13	0.17
D.I.	Bupivacaine	0.81	0.92	-0.24	-0.39	-0.30
I.W.		1.42	1.62	-0.93	-0.82	-0.60
A.G.		3.40	3.04	-2.16	-2.04	-1.73
K.C. +		1.24	0.97	-0.47	-0.49	-0.10
R.G. +		2.89	2.21	-0.63	-0.67	-1.08
N.T. +		1.73	2.05	-0.86	-0.70	-0.59
Mean		1.91	1.80	-0.88	-0.85	-0.73
SEM		0.43	0.32	0.27	0.24	0.51
D.I.	Sodium Cromoglycate	0.82	0.86	-0.19	-0.22	-0.32
I.W.		1.86	1.97	-1.09	-1.12	-1.03
A.G.		2.15	2.36	-1.06	-0.94	-0.92
K.C. +		1.53	1.52	-0.70	-0.53	-0.41
R.G. +		2.15	2.17	-1.45	-0.88	-0.74
N.T. +		1.97	1.97	-0.58	-0.74	-0.69
Mean		1.75	1.80	-0.84	-0.74	-0.68
SEM		0.33	0.22	0.18	0.13	0.11

+ Subjects with upper respiratory tract infection
* Values significantly different from those with saline pre-treatment at that time ($p < 0.05$)
B, before pre-treatment; A, after saline, ipratropium, bupivacaine, or sodium cromoglycate

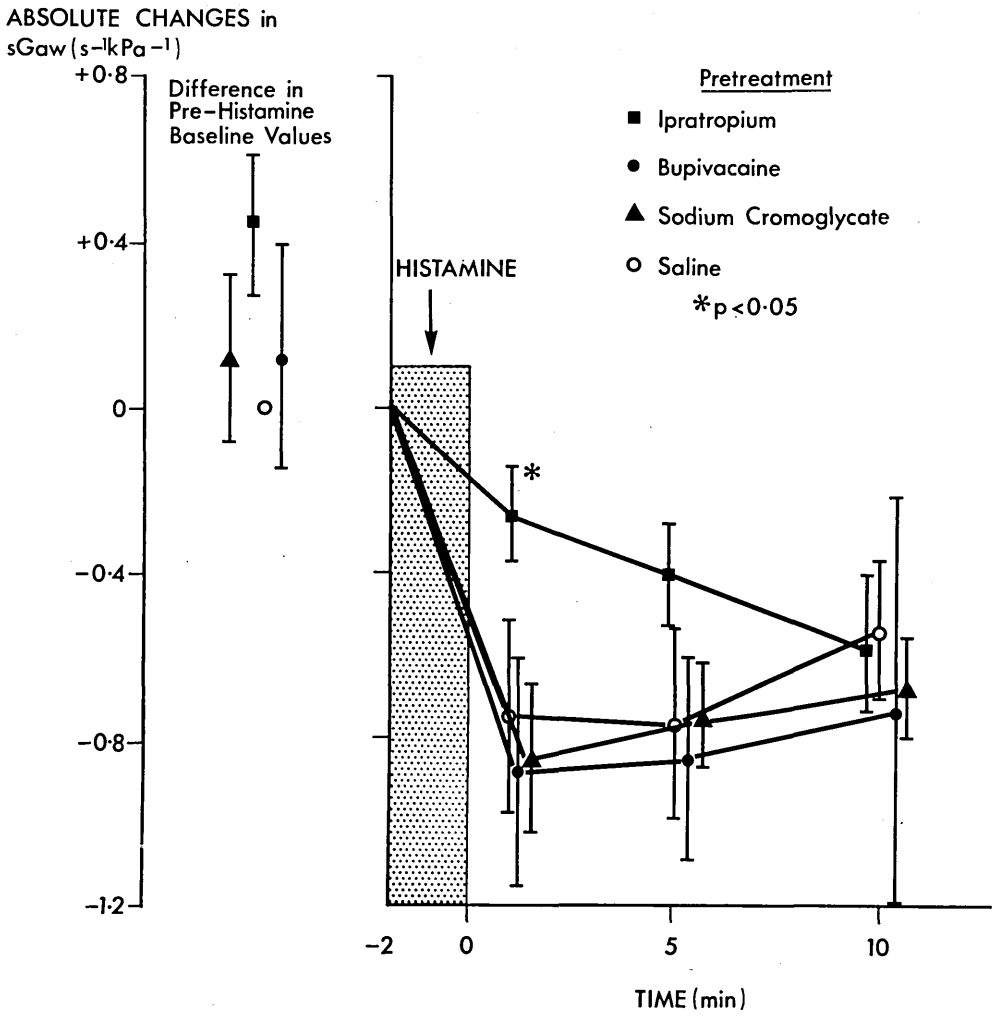

FIGURE 19 EFFECT OF INHALED HISTAMINE ON sGaw FOLLOWING IPRATROPIUM, BUPIVACAINE, SODIUM CROMOGLYCATE OR SALINE IN NORMAL SUBJECTS (N = 6)

TABLE XX Effect of inhaled prostaglandin on sGaw following ipratropium, bupivacaine, sodium cromoglycate or saline in normal subjects (N=5)

Subject	Pre-treatment	Baseline sGaw ($s^{-1}kPa^{-1}$) B	Baseline sGaw ($s^{-1}kPa^{-1}$) A	Change in sGaw after prostaglandin (0.5 g/l) 1 min	Change in sGaw after prostaglandin (0.5 g/l) 5 min
K.C.	Saline	2.42	1.81	-0.72	-0.65
D.I.		1.00	0.97	-0.14	-0.31
I.W.		1.25	1.34	-0.39	-0.93
K.P.		3.10	2.44	-0.94	-0.96
A.G.		1.64	1.92	-1.12	-0.68
Mean		1.88	1.69	-0.66	-0.70
SEM		0.38	0.25	0.17	0.11
K.C.	Ipratropium	1.13	1.71	-0.47	-0.55
D.I.		1.15	1.20	-0.16	-0.37
I.W.		0.75	1.02	-0.02	-0.44
K.P.		3.35	4.66	-0.16	-0.51
A.G.		2.47	4.20	-1.51	-2.47
Mean		1.77	2.55	-0.46	-0.87
SEM		0.49	0.77	0.27	0.40
K.C.	Bupivacaine	0.98	0.98	-0.21	-0.30
D.I.		0.87	0.88	-0.06	-0.34
I.W.		1.36	1.36	-0.51	-0.93
K.P.		3.20	3.54	-1.73	-1.82
A.G.		2.60	2.47	-0.99	-1.38
Mean		1.80	1.84	-0.70	-0.95
SEM		0.46	0.50	0.30	0.29

B, before pre-treatment; A, after saline, ipratropium or bupivacaine
* Values significantly different from those with saline pre-treatment at that time ($p < 0.05$)

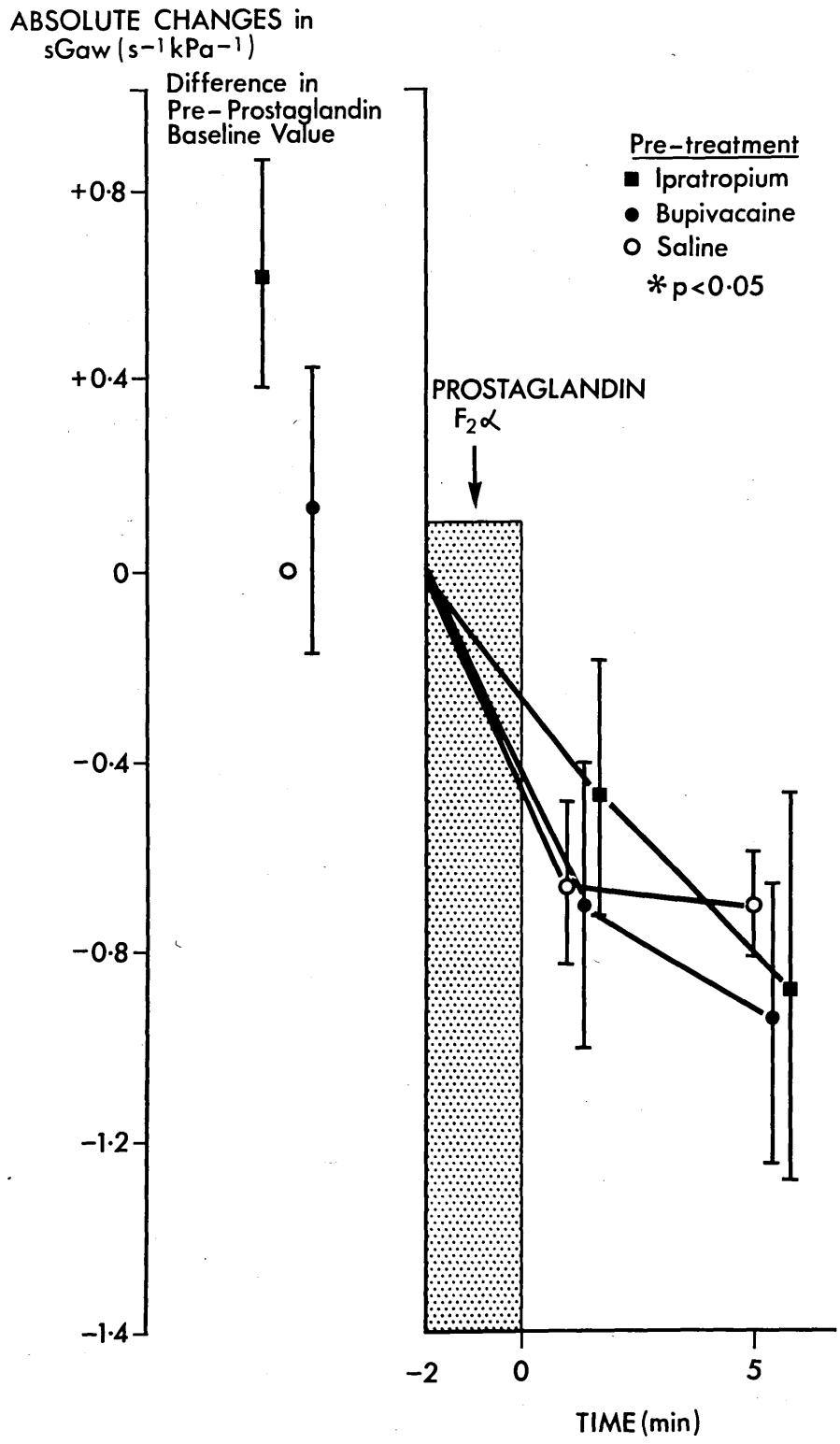

FIGURE 20 EFFECT OF INHALED PROSTAGLANDIN $F_2\alpha$ ON sGaw FOLLOWING IPRATROPIUM, BUPIVACAINE OR SALINE IN NORMAL SUBJECTS (N = 5)

TABLE XXI Effect of inhaled cigarette smoke on sGaw following ipratropium, bupivacaine, sodium cromoglycate or saline in normal subjects (N=8)

Subject	Age	Sex	Pre-treatment	Baseline sGaw ($s^{-1}kPa^{-1}$) B	Baseline sGaw ($s^{-1}kPa^{-1}$) A	Change in sGaw after cigarette smoke 2 min
RJ	23	F	Saline	2.14	2.21	-0.53
KR	28	F		1.80	2.01	-0.25
MS	27	F		3.41	3.89	-1.12
AL	24	F		2.89	2.83	-1.04
WF	27	F		1.93	2.08	-0.68
YI	23	F		0.87	1.02	-0.16
LF	22	F		1.04	1.05	-0.10
IW	37	M		1.06	1.06	-0.28
Mean				1.89	2.01	-0.52
SEM				0.32	0.35	0.13
RJ			Sodium Cromoglycate	3.06	3.50	-1.13
KR				2.51	2.71	-0.79
MS				3.44	3.61	-0.91
AL				2.30	2.59	-1.07
WF				2.16	1.40	-0.33
YI				1.00	1.30	-0.03
LF				1.47	1.07	-0.29
IW				1.18	1.21	-0.16
Mean				2.13	2.17	-0.58
SEM				0.31	0.37	0.15
RJ			Ipratropium	3.49	4.07	+0.17
KR				1.86	3.18	-0.06
MS				3.17	5.42	+0.22
AL				2.48	3.70	-0.28
WF				1.28	1.62	-0.08
YI				0.88	1.13	-0.25
LF				1.38	2.00	+0.66
IW				1.21	1.27	-0.00
Mean				1.96	2.80	-0.04*
SEM				0.34	0.54	0.10
RJ			Bupivacaine	2.92	2.38	-0.57
KR				2.20	1.81	-0.15
MS				3.50	3.45	-0.91
AL				2.50	2.50	-0.64
WF				1.49	1.38	-0.22
YI				1.01	1.03	-0.26
LF				1.13	0.81	-0.10
IW				0.91	0.96	-0.04
Mean				1.95	1.79	-0.36
SEM				0.34	0.32	0.10

B, before pre-treatment; A, after saline, sodium cromoglycate, ipratropium or bupivacaine

* Values significantly different from those with saline pre-treatment ($p < 0.05$)

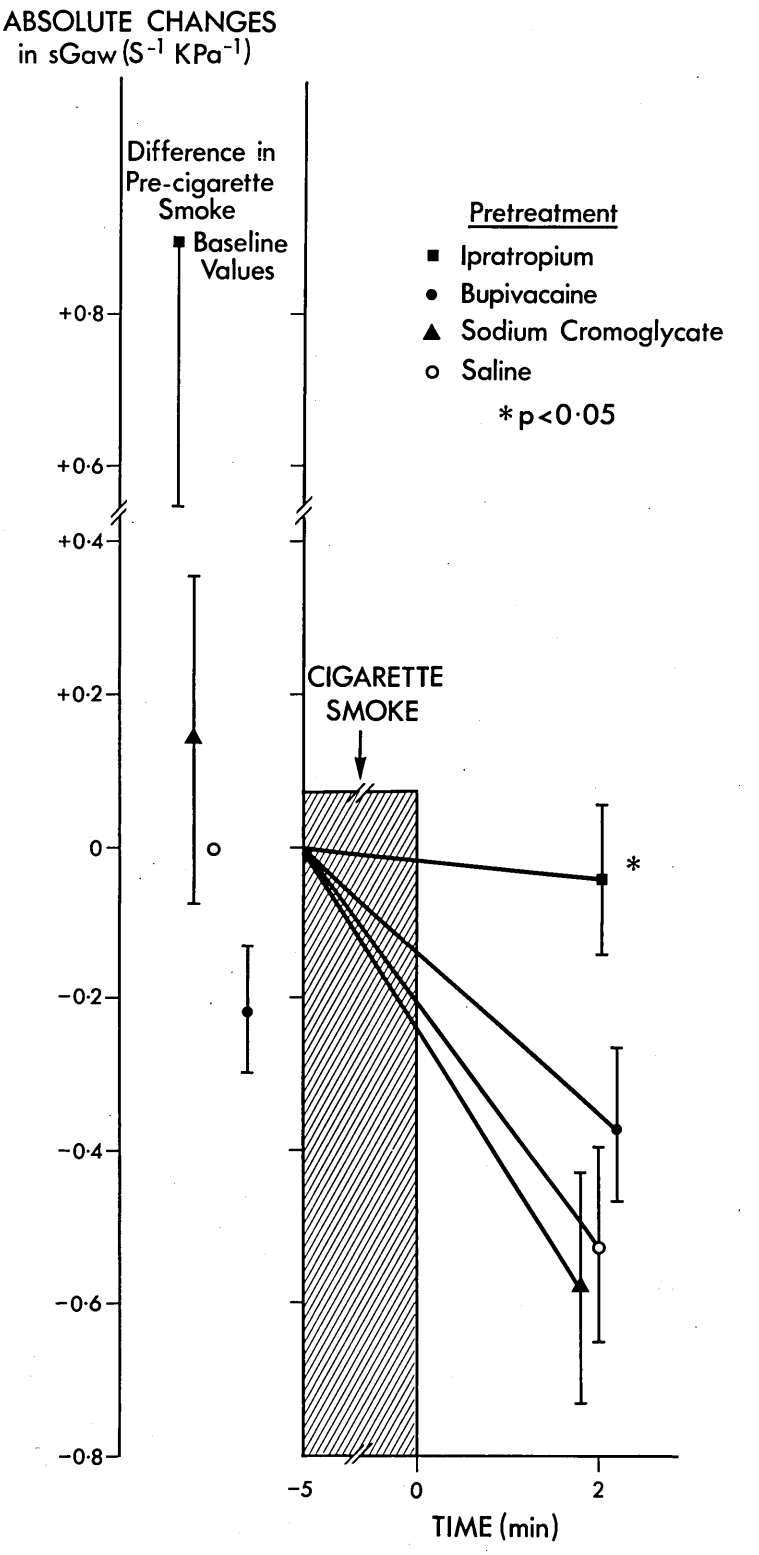

FIGURE 21 EFFECT OF INHALED CIGARETTE SMOKE ON sGaw FOLLOWING IPRATROPIUM, BUPIVACAINE, SODIUM CROMOGLYCATE OR SALINE IN NORMAL SUBJECTS (N = 8)

CHAPTER VI

EFFECT OF INHALED HIGH DOSE ANTICHOLINERGIC DRUGS IN PREVENTION OF EXERCISE-INDUCED ASTHMA

INTRODUCTION

Exercise-induced asthma (EIA) may be due to reflex vagal bronchoconstriction secondary to stimulation of irritant receptors. Circumstantial evidence for reflex bronchoconstriction occurring in EIA is based on blocking efferent motor actions by anticholinergic drugs. The protective action of cholinergic blocking drugs is, however, variable (Table I), although the lack of inhibition of EIA in some studies may be due to insufficient cholinergic blockade (Tinkelman et al, 1976).

The purpose of this study was to investigate the effects of the anticholinergic drugs ipratropium bromide and atropine sulphate in the prevention of EIA.

METHODS

Nine patients with extrinsic asthma were studied (Table XXII). FEV_1 was measured in triplicate using a dry wedge spirometer (Vitalograph), the best recording being used for analysis. Exercises were performed on an inclined treadmill as previously described. The study was completed within seven days.

After baseline measurements of FEV_1, the following agents were administered by Wright nebuliser during 10 min tidal breathing; Saline (9 g/l, 0.15 mol/l); ipratropium bromide (0.25 g/l, 0.6 mmol/l) - estimated

TABLE XXII Clinical details of asthmatic patients

Patient No		Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean baseline FEV_1 (l)	% Predicted FEV_1
1	E.I.	36	F	167	65	2.25	76.2
2	R.McC.	31	F	158	60	2.62	90.3
3	R.C.	19	M	160	60	2.74	76.1
4	L.McG.	18	F	150	52	2.04	75.5
5	A.K.	18	M	162	60	2.89	78.1
6	E.H.	27	F	150	55	2.12	78.5
7	P.R.	21	M	170	62	4.54	113.5
8	H.M.	20	F	165	60	3.30	103.1
9	R.G.	35	M	180	89	3.85	96.2

dose nebulised 0.5 mg (1.2 μmol); atropine sulphate (5 g/l, 7.1 mmol/l) - estimated dose nebulised 10 mg (14.2 μmol).

After 20 min spirometry was repeated and then at 5, 10 and 20 min after the exercise test. A positive response was defined as one in which there was a decrease in FEV_1 of more than 20%. Saline and ipratropium bromide were given in a random single blind manner to all the patients, while atropine sulphate was given to only four patients (Nos 4, 5, 6, 9).

Statistical analysis was performed using "Student's" paired t test.

RESULTS (Table XXIII, Figures 22, 23)

There was no significant difference between the baseline values before aerosol administration on the two days. Ipratropium bromide produced a significant increase in FEV_1 ($P < 0.01$) whereas there was no significant difference in FEV_1 following saline. In the nine asthmatics studied ipratropium bromide had no protective effect on exercise-induced asthma when assessed as either the maximum absolute fall in FEV_1 or the maximum percentage fall in FEV_1. However, five (Nos 1, 2, 3, 7, 8) of the nine asthmatics studied developed less than a 15% fall in FEV_1 after exercise following pre-treatment with ipratropium bromide, while all the subjects showed a greater than 20% fall in FEV_1 after exercise following pre-treatment with saline. No side effects were noted after the inhalation of

ipratropium bromide.

In the four asthmatics (Nos 4, 5, 6, 9) in whom a greater than 15% fall in FEV_1 after exercise occurred following pretreatment with ipratropium bromide, atropine sulphate also did not inhibit EIA. All subjects experienced a dry mouth following the inhalation of atropine sulphate.

Detailed results for each patient are tabulated in Appendix D, Table LXVI.

DISCUSSION

The dose of atropine sulphate required in animals to block bronchoconstriction induced by stimulation of the vagi is between 0.5 mg/Kg to 2.0 mg/Kg body weight, which is higher than could be safely given to humans (Widdicombe & Stirling, 1970). Tinkelman et al, (1976) have suggested that the variable effect of anticholinergic drugs in preventing EIA could be due to insufficient cholinergic blockade. These authors reported that pre-treatment with 0.1 mg/Kg body weight of inhaled atropine sulphate prevented EIA in 17 out of 18 asthmatic patients. Unfortunately, in that study the percentage fall in spirometric measurements after exercise was calculated from the pre-treatment value, and not from the higher value following the bronchodilation produced by atropine sulphate. In the present study, the failure of high dose atropine sulphate (approximate dose 0.15 mg/Kg body weight) or

ipratropium bromide to prevent EIA in four asthmatic patients, despite causing bronchodilation, suggests that in these patients cholinergic mechanisms are unlikely to have been important in the pathogenesis of EIA. However, the inhibitory effect of an even higher concentration of atropine on EIA cannot be completely excluded. The partial reduction of EIA with ipratropium bromide in the other five patients may indicate that vagal mechanisms are important in these subjects, or alternatively, the bronchodilation from ipratropium bromide may have resulted in reduced bronchial reactivity, due to a change in baseline airflow obstruction (Benson, 1975).

It is concluded that the lack of inhibition of EIA in some patients following anticholinergic drugs is probably not due to insufficient cholinergic blockade. This may indicate that mechanisms other than reflex vagal bronchoconstriction are involved in the pathogenesis of EIA.

TABLE XXIII Maximum fall in FEV_1 after exercise following ipratropium, atropine or saline

Patient No	CONTROL Baseline B	CONTROL Baseline A	CONTROL % fall	CONTROL Absolute fall (l)	IPRATROPIUM BROMIDE Baseline B	IPRATROPIUM BROMIDE Baseline A	IPRATROPIUM BROMIDE % fall	IPRATROPIUM BROMIDE Absolute fall (l)	ATROPINE SULPHATE Baseline B	ATROPINE SULPHATE Baseline A	ATROPINE SULPHATE % fall	ATROPINE SULPHATE Absolute fall (l)
1	2.18(77.8)	2.23(79.6)	-31.3	-0.70	2.32(82.8)	2.68(95.7)	- 8.5	-0.23				
2	2.63(75.1)	2.61(74.5)	-24.0	-0.63	2.61(74.5)	3.06(87.4)	- 6.8	-0.21				
3	2.75(72.3)	2.88(75.7)	-46.0	-1.33	2.73(71.8)	3.13(82.3)	-12.1	-0.38				
4	2.03(75.1)	1.95(72.2)	-41.0	-0.90	2.08(77.0)	2.68(99.2)	-33.2	-0.89	2.03(75.1)	2.71(100.0)	-50.9	-1.38
5	3.01(79.2)	3.01(79.2)	-66.1	-1.99	2.96(77.8)	3.33(87.6)	-66.3	-2.21	2.70(71.0)	3.29(86.5)	-59.2	-1.95
6	2.03(75.1)	2.01(74.4)	-32.8	-0.66	2.10(77.7)	2.48(91.8)	-31.0	-0.77	2.23(82.5)	2.53(93.7)	-52.1	-1.32
7	4.56(114.8)	4.73(119.1)	-30.6	-1.45	4.51(113.6)	4.62(116.3)	- 0.6	-0.03				
8	3.26(102.1)	3.34(95.5)	-20.0	-0.67	3.34(104.7)	3.56(111.5)	- 7.5	-0.27				
9	3.84(94.3)	3.85(94.5)	-40.5	-1.56	3.90(95.8)	4.40(108.1)	-69.5	-3.06	3.80(93.3)	4.50(110.5)	-69.1	-3.11
Mean	2.92(85.0)	2.95(84.9)	-36.9	-1.08	2.95(86.1)	3.32(97.7)	-26.1	-0.89	2.69(80.4)	3.25(97.6)	-57.8	-1.94
SEM	0.28(5.0)	0.30(5.1)	4.5	0.16	0.27(4.9)	0.25(3.9)	8.6	0.34	0.39(4.8)	0.44(5.0)	4.1	0.41
t							1.69	0.70				
P value							NS	NS				

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

B, before pre-treatment; A, after saline, ipratropium bromide or atropine sulphate

Percentage and absolute fall in FEV_1 are calculated from baseline (A)

P values refer to the difference between results after control exercise and those after ipratropium or atropine

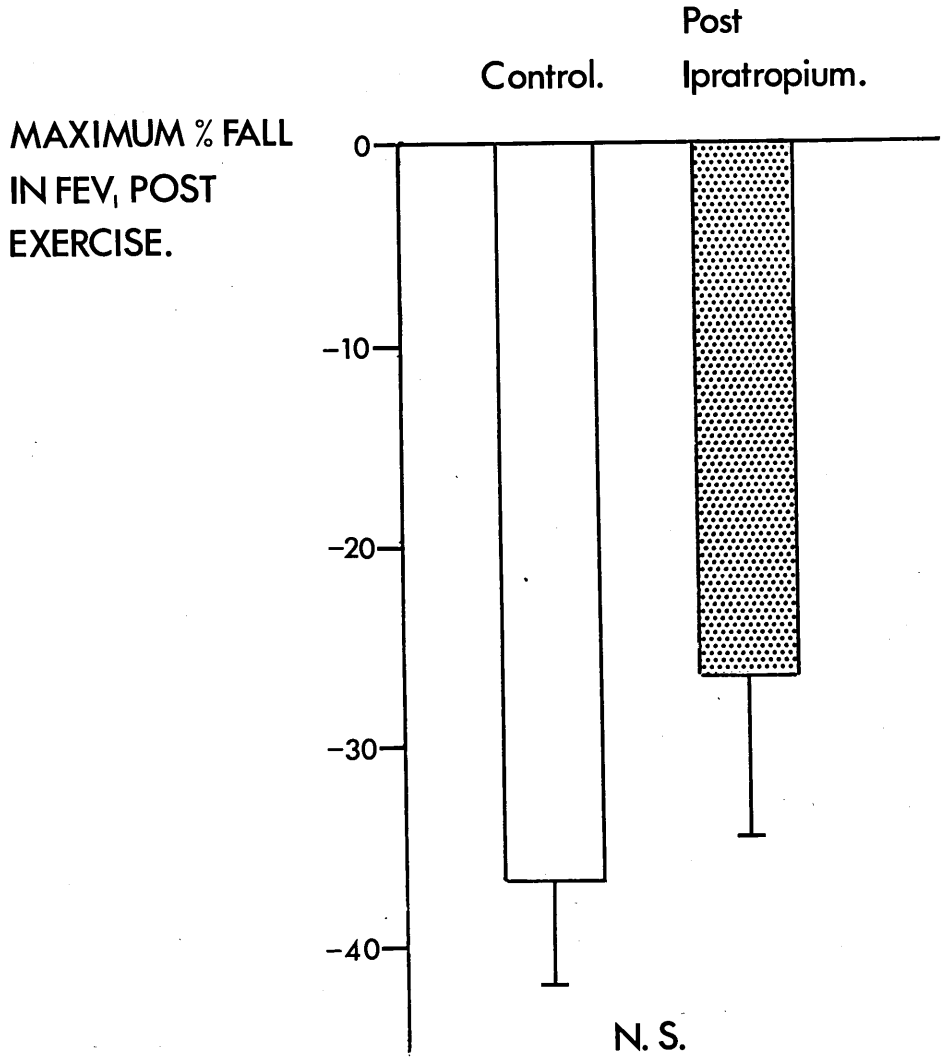

FIGURE 22 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FEV_1 AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING IPRATROPIUM OR SALINE IN ASTHMATIC PATIENTS (N = 9)

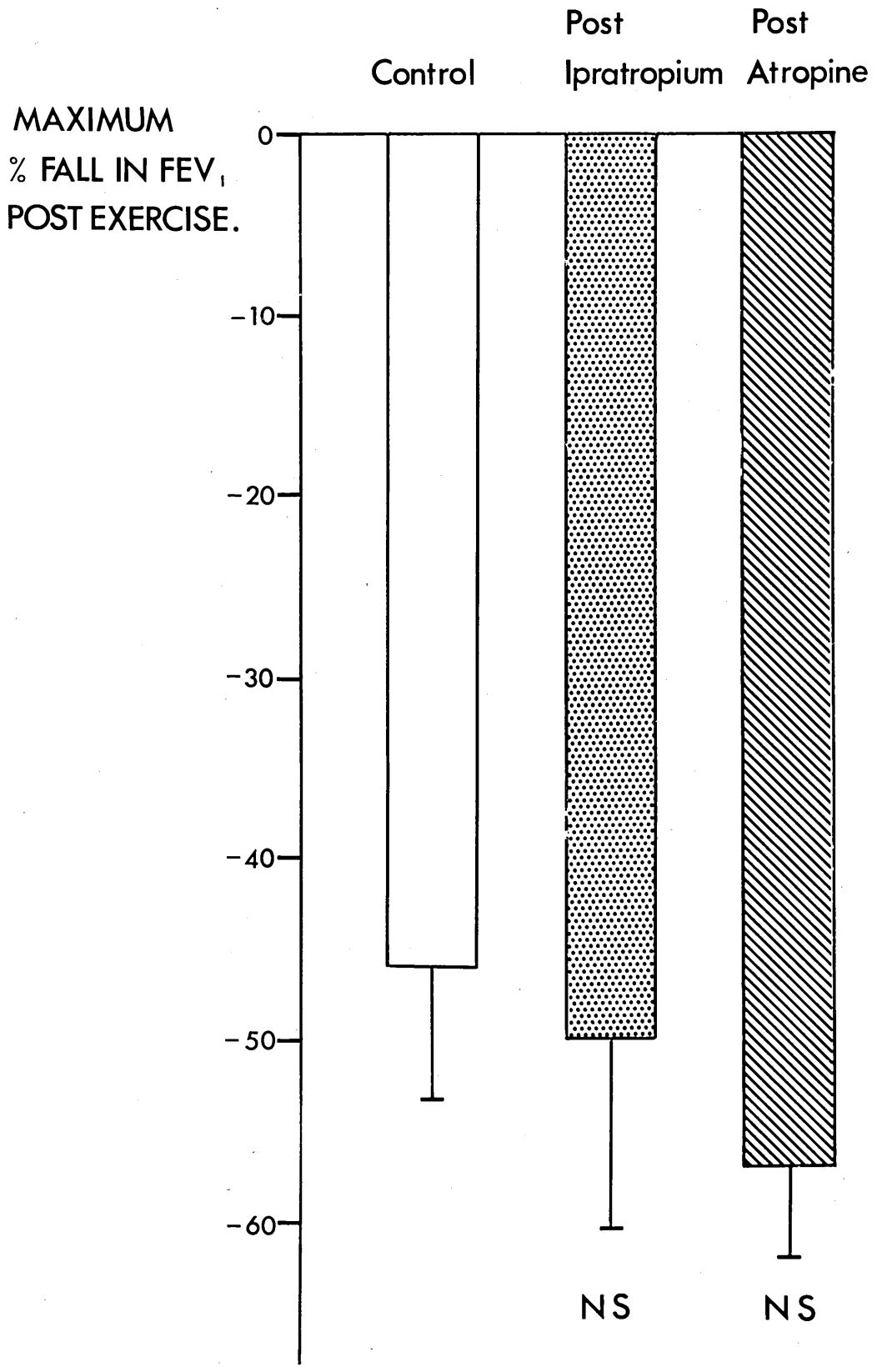

FIGURE 23 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FEV_1 AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING IPRATROPIUM, ATROPINE OR SALINE IN ASTHMATIC PATIENTS (N = 4)

CHAPTER VII

EFFECT OF SODIUM CROMOGLYCATE AND IPRATROPIUM BROMIDE IN PREVENTION OF EXERCISE-INDUCED ASTHMA

INTRODUCTION

Although the mechanisms involved in exercise-induced asthma (EIA) are unknown, both the release of bronchoconstrictor mediators (Godfrey, 1975) and reflex bronchoconstriction secondary to stimulation of vagal receptors (Gold, 1975) have been postulated. Sodium cromoglycate (SCG), which inhibits the release of mediators from mast cells (Orr et al, 1970), may have a preventive effect in EIA through a similar machanism (Davies, 1968). Circumstantial evidence supporting the hypothesis that reflex vagal bronchoconstriction is implicated in the pathogenesis of EIA is based on the inhibitory effects of anticholinergic drugs. However, the results of the previous experiment (Chapter VI) suggest that the lack of inhibition of EIA in some patients following anticholinergic drugs is unlikely to be due to insufficient cholinergic blockade. In an uncontrolled study reported by McFadden et al, (1977[b]) the combination of SCG and the anticholinergic drug ipratropium bromide (IB) inhibited EIA in all patients studied, whereas IB alone inhibited only those patients with mainly large airways obstruction as assessed by changes in density dependence of maximal expiratory flow rates. SCG was not given alone. They concluded that the airway response to exercise in asthmatics is heterogeneous in terms of predominant site of flow limitation and with regard to mechanism.

The purpose of this study was, therefore, to

investigate in a double blind manner the effects of SCG, IB and IB plus SCG in the prevention of EIA in patients whose main site of airflow obstruction was in small and large airways as assessed by maximal expiratory flow rate response to low density gas breathing. It was hoped that these results might further define the role of mediator release and vagal action in EIA.

METHODS

Thirteen patients with extrinsic asthma were studied (Table XXIV). FEV_1, FVC and MMEF were measured in triplicate using a water-sealed spirometer (Godart), the best recording being used for analysis. MEFV curves were produced with the patient breathing air, and then an $He-O_2$ mixture as previously described. Predicted normal values were taken from Cotes (1975) for FEV_1 and FVC and from Cherniak & Raber (1972) for MMEF. Exercises were performed on an inclined treadmill as previously described. The four exercise tests performed on each patient were all completed within 10 days.

The studies were carried out in a random double-blind fashion using the following agents administered by a Wright nebuliser during 10 min tidal breathing: (1) SCG nebuliser solution (10 g/l, 19.5 mmol/l) - estimated dose nebulised 20 mg (39.0 μmol); (2) IB (1 g/l, 2.4 mmol/l) - estimated dose nebulised 2.0 mg (4.8 μmol); (3) SCG (10 g/l, 19.5 mmol/l) + IB (1 g/l, 2.4 mmol/l) solutions; and (4) saline solution (9 g/l, 0.15 mol/l). Following baseline measurements of FEV_1

TABLE XXIV Clinical details of asthmatic patients

Patient No	Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean Baseline FEV_1 (l)	% Predicted FEV_1
1 V.D.	25	F	159	62	3.19	104.5
2 C.W.	18	F	152	52	2.49	87.3
3 E.T.	31	F	169	75	2.72	87.1
4 F.O'D.	33	M	169	65	2.64	71.7
5 A.F.	21	M	187	71	4.92	106.5
6 F.H.	20	F	166	60	3.29	102.8
7 M.D.	18	M	170	74	3.31	83.1
8 E.P.	18	F	161	73	2.85	91.9
9 A.H.	32	M	186	79	3.03	69.1
10 S.S.	32	F	171	74	3.24	101.2
11 W.K.	17	M	142	53	3.35	101.5
12 J.M.	24	M	163	66	1.69	44.7
13 A.K.	18	M	162	60	1.75	47.3

FVC, MMEF and MEFV curves breathing air and He-O_2, the drug solution was inhaled for two periods of five minutes separated by an interval of one minute. After 20 minutes spirometry was repeated, and then at 2, 5, 10, 15 and 20 min after the exercise test. In three patients (Nos 4, 8, 10) MEFV curves breathing air and He-O_2 were also recorded between 5 and 10 min post exercise. A positive response was defined as one in which there was a decrease in FEV_1 of more than 20%. Results of exercise tests were expressed as the maximum percentage and absolute fall in lung function after exercise compared to the post-drug or placebo baseline.

Statistical analysis was performed using "Student's" paired and unpaired t tests.

RESULTS

In eight of the 13 patients studied, the mean baseline ratio $\dot{V}_{50He}/\dot{V}_{50AIR}$ was over 1.20, and these were called responders; the remaining five patients were called non-responders (Table XXV). Hereafter, the results are referred to in these two groups.

The results of the tests are given in Tables XXVI, XXVII, XXVIII and Figures 24, 25, 26.

There was no significant difference between the baseline values of FEV_1, FVC and MMEF before aerosol administration on the four days. Mean baseline MMEF was significantly lower in non-responders ($P < 0.02$),

but there were no significant differences in FEV_1 or FVC. There was no differences between the falls in ventilatory capacity after the control exercise in the two groups.

SCG, IB and IB plus SCG all significantly inhibited the percentage and absolute fall in FEV_1 after exercise in the responders. IB, however, had no protective action in the non-responders, unlike both SCG and IB plus SCG. IB had no significant effect on FVC after exercise in the non-responders. SCG significantly prevented the percentage and absolute fall in MMEF in both responders and non-responders (percentage fall only), while IB had no protective action in either group. In responders the drugs shown to have a significant inhibitory action were equally effective in preventing the fall in FEV_1 and MMEF. In addition, there was no difference between SCG and SCG plus IB in the non-responders.

In the three patients (Nos 4, 8, 10) in whom $\dot{V}_{50He}/\dot{V}_{50AIR}$ was measured after exercise, the ratio increased in one from 1.29 to 1.35(No 4), in another it fell from 1.57 to 1.00 (No 8), while in the third it remained 1.00 (No 10). These post-exercise values all refer to post IB exercise.

No side effects were noted during the study after any of the drugs used.

Detailed results for each patient are tabulated in Appendix D, Tables LXVI - LXXVII.

TABLE XXV Baseline ratio $\dot{V}_{50}$He to $\dot{V}_{50}$Air

Patient No	Saline B	Sodium Cromoglycate B	Ipratropium Bromide B	Ipratropium Bromide plus Sodium Cromoglycate B	Mean Ratio
1	1.44	1.45	1.40	1.49	1.44
2	1.23	1.35	1.29	1.28	1.28
3	1.22	1.22	1.34	1.30	1.27
4	1.20	1.22	1.29	1.25	1.22
5	1.44	1.42	1.32	1.28	1.36
6	1.27	1.25	1.32	1.30	1.28
7	1.26	1.26	1.30	1.39	1.30
8	1.57	1.43	1.57	1.56	1.53
9	0.99	1.02	1.06	1.01	1.02
10	1.00	1.03	1.00	1.00	1.00
11	0.97	1.03	1.03	0.97	1.00
12	1.07	1.04	1.05	1.09	1.06
13	1.01	1.01	1.03	1.00	1.01

B - before drug

TABLE XXVI Maximum fall in FEV_1 after exercise following sodium cromoglycate, ipratropium bromide or ipratropium bromide plus sodium cromoglycate

Patient No	CONTROL Baseline B	CONTROL Baseline A	CONTROL % fall	CONTROL Absolute fall (l)	SODIUM CROMOGLYCATE Baseline B	SODIUM CROMOGLYCATE Baseline A	SODIUM CROMOGLYCATE % fall	SODIUM CROMOGLYCATE Absolute fall (l)	IPRATROPIUM BROMIDE Baseline B	IPRATROPIUM BROMIDE Baseline A	IPRATROPIUM BROMIDE % fall	IPRATROPIUM BROMIDE Absolute fall (l)	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Baseline B	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Baseline A	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE % fall	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Absolute fall (l)
Responders																
1	3.51(115.0)	3.52(115.4)	-26.1	-1.27	3.11(101.9)	2.95(96.7)	-20.7	-0.61	2.92(95.7)	3.44(112.7)	-16.0	-0.55	3.24(106.2)	3.69(120.9)	-12.5	-0.46
2	2.52(88.4)	2.52(88.4)	-50.0	-1.26	2.28(80.0)	2.39(83.8)	+ 8.3	+0.20	2.68(94.0)	2.74(96.1)	-18.2	-0.50	2.94(87.3)	2.76(96.8)	- 5.8	-0.16
3	2.69(86.2)	2.93(93.9)	-20.9	-0.61	2.74(87.8)	2.91(93.2)	-17.6	-0.51	2.80(89.7)	2.93(93.9)	- 3.5	-0.10	2.68(85.8)	2.78(89.1)	- 5.1	-0.14
4	2.85(77.4)	2.68(72.8)	-51.1	-1.37	2.60(70.6)	2.40(65.2)	-18.4	-0.44	2.89(78.5)	3.19(86.6)	- 1.0	-0.03	2.23(60.5)	3.04(82.6)	+ 3.6	+0.11
5	4.86(105.1)	4.75(102.8)	-25.5	-1.21	5.07(109.7)	4.87(105.4)	- 3.3	-0.16	4.80(103.8)	5.24(113.4)	-14.9	-0.78	4.95(107.1)	5.05(109.3)	+ 0.7	+0.04
6	3.13(97.8)	3.19(99.6)	-20.4	-0.65	3.21(100.3)	3.48(108.7)	- 6.7	-0.23	3.51(109.6)	3.47(108.4)	- 7.8	-0.27	3.31(103.4)	3.43(107.1)	- 3.3	-0.11
7	3.20(80.4)	3.20(80.4)	-34.4	-1.10	3.43(86.1)	3.67(92.2)	-38.2	-1.40	3.51(88.1)	3.45(86.6)	-31.6	-1.09	3.11(78.1)	3.69(92.7)	-37.7	-1.39
8	2.87(92.5)	3.14(101.2)	-71.1	-2.23	2.84(91.6)	3.38(109.0)	-42.9	-1.45	2.34(75.4)	3.10(100.0)	-56.2	-1.74	3.35(108.0)	3.28(105.8)	-19.6	-0.64
Mean	3.20(92.8)	3.24(94.3)	-38.7	-1.21	3.16(91.0)	3.23(94.2)	-17.5	-0.57	3.14(92.2)	3.42(99.7)	-18.7	-0.63	3.15(92.0)	3.44(100.5)	-10.0	-0.34
SEM	0.26 4.4	0.24 4.7	6.2	0.17	0.30 4.4	0.28 5.2	6.0	0.20	0.27 4.1	0.27 3.8	6.3	0.20	0.29 6.0	0.26 4.4	4.7	0.17
t							2.83	3.23			3.51	4.28			3.76	3.95
P value							<0.05	<0.02			<0.01	<0.01			<0.01	<0.01
Non-responders																
9	3.08(70.3)	3.15(72.6)	-41.0	-1.29	3.30(75.3)	3.74(85.3)	- 3.5	-0.13	3.19(72.6)	4.20(96.8)	-49.5	-2.08	2.57(58.6)	4.03(92.0)	- 8.2	-0.33
10	3.25(101.5)	3.25(101.5)	-56.3	-1.83	3.28(102.5)	2.88(90.0)	- 0.0	-0.00	3.23(100.9)	3.43(107.1)	-42.3	-1.45	3.22(100.6)	3.59(112.1)	+ 2.7	+0.10
11	3.68(111.5)	3.63(110.0)	-30.6	-1.11	3.38(102.4)	3.38(102.4)	- 3.0	-0.10	2.83(85.7)	3.69(111.8)	-26.6	-0.98	3.53(106.9)	3.95(119.6)	- 1.3	-0.05
12	1.67(44.1)	1.71(45.2)	-23.4	-0.40	1.57(41.5)	1.67(44.1)	-12.0	-0.20	1.58(41.7)	1.91(50.5)	-43.5	-0.83	1.94(51.3)	2.14(56.6)	+ 7.9	+0.04
13	1.86(50.2)	1.75(47.2)	-34.2	-0.60	1.63(44.0)	1.85(50.0)	-30.8	-0.57	2.04(55.1)	2.03(54.8)	-31.6	-0.62	1.47(39.7)	1.67(45.1)	-24.0	-0.43
Mean	2.70(75.5)	2.69(75.3)	-37.1	-1.04	2.63(73.1)	2.65 74.3	- 9.8	-0.20	2.54(71.2)	3.00(84.2)	-38.7	1.19	2.54(71.4)	3.03(85.0)	- 4.6	-0.13
SEM	0.39 13.4	0.40 13.4	5.5	0.25	0.42 13.3	0.40 11.5	5.6	0.09	0.32 10.5	0.45 13.1	4.1	0.26	0.38 13.5	0.48 14.7	5.5	0.10
t							2.89	2.78			0.27	0.70			4.17	3.01
P value							<0.05	<0.05			NS	NS			<0.02	<0.05

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

B, before pre-treatment; A, after saline, sodium cromoglycate, ipratropium bromide or ipratropium bromide plus sodium cromoglycate

Percentage and absolute fall in FEV_1 after exercise are calculated from baseline (A)

P values refer to the difference between results after control exercise and those after sodium cromoglycate or ipratropium bromide or ipratropium bromide plus sodium cromoglycate

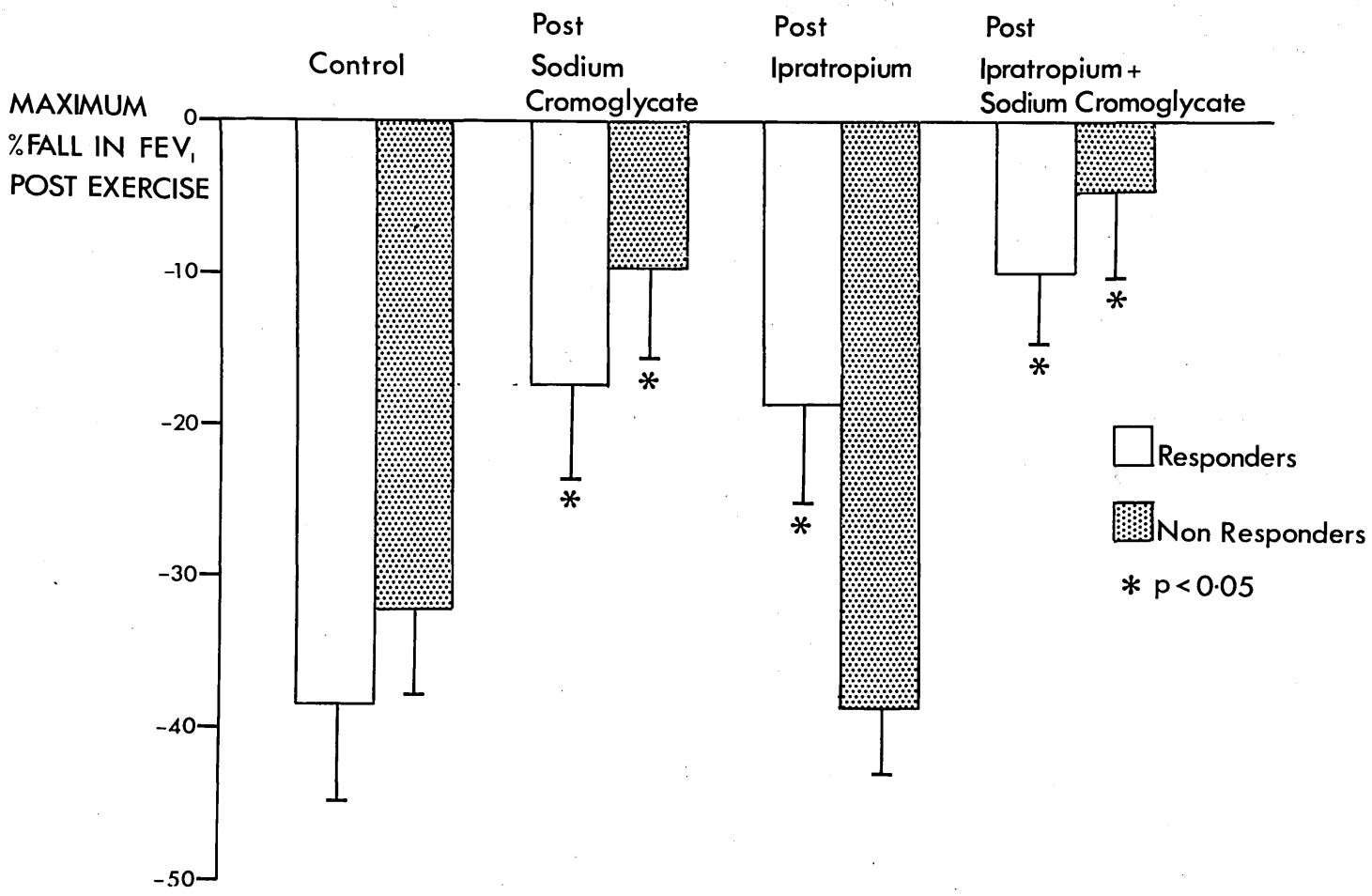

FIGURE 24 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FEV_1 AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING SODIUM CROMOGLYCATE, IPRATROPIUM, IPRATROPIUM PLUS SODIUM CROMOGLYCATE OR SALINE IN RESPONDERS (N = 8) AND NON-RESPONDERS (N = 5)

TABLE XXVII Maximum fall in FVC after exercise following sodium cromoglycate, ipratropium bromide or ipratropium bromide plus sodium cromoglycate

Patient No	CONTROL Baseline B	CONTROL Baseline A	CONTROL % fall	CONTROL Absolute fall (l)	SODIUM CROMOGLYCATE Baseline B	SODIUM CROMOGLYCATE Baseline A	SODIUM CROMOGLYCATE % fall	SODIUM CROMOGLYCATE Absolute fall (l)	IPRATROPIUM BROMIDE Baseline B	IPRATROPIUM BROMIDE Baseline A	IPRATROPIUM BROMIDE % fall	IPRATROPIUM BROMIDE Absolute fall (l)	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Baseline B	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Baseline A	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE % fall	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Absolute fall (l)
Responders																
1	4.40(122.2)	4.40(122.2)	-15.0	-0.66	4.15(115.2)	4.08(113.3)	- 8.1	-0.33	4.38(121.6)	4.17(111.1)	+ 3.5	+0.15	4.31(119.7)	4.59(127.5)	- 5.9	-0.27
2	3.28(105.8)	3.28(105.8)	-36.0	-1.18	2.99(96.4)	2.92(94.1)	+ 5.8	+0.17	3.30(106.4)	3.13(100.9)	- 2.6	-0.08	3.09(99.6)	3.31(106.7)	- 9.7	-0.32
3	3.56(91.7)	3.69(95.1)	-11.7	-0.43	3.38(87.1)	3.62(93.2)	-14.1	-0.51	3.71(95.6)	3.67(94.5)	- 0.9	-0.06	3.43(88.4)	3.38(87.1)	- 1.5	-0.05
4	3.58(80.4)	3.48(78.2)	-40.3	-1.40	3.55(79.7)	3.21(72.1)	-16.9	-0.54	3.80(85.3)	3.59(80.6)	+ 0.0	+0.00	2.98(66.9)	3.65(82.0)	+ 4.6	+0.17
5	6.17(110.1)	6.10(108.9)	-18.7	-1.14	5.78(103.2)	5.68(101.4)	- 6.0	-0.44	5.88(105.0)	6.05(108.0)	- 5.2	-0.31	5.86(104.6)	5.99(106.9)	- 1.1	+0.09
6	3.82(97.9)	3.93(100.7)	-10.2	-0.40	3.98(102.0)	4.08(104.6)	- 1.5	-0.05	4.02(103.0)	3.98(102.0)	- 2.6	-0.10	3.97(101.7)	4.04(103.5)	- 1.0	-0.04
7	4.30(91.4)	4.35(92.5)	-13.8	-0.60	4.70(100.0)	4.79(101.9)	-27.0	-1.29	4.55(96.8)	4.59(97.6)	- 9.6	-0.44	4.77(99.3)	4.80(102.1)	-15.9	-0.76
8	4.20(116.6)	4.17(115.8)	-66.7	-2.78	3.96(110.0)	4.40(122.2)	-36.2	-1.59	3.34(92.7)	3.99(110.8)	-49.4	-1.75	4.52(125.5)	4.39(121.9)	- 9.4	-0.36
Mean	4.16(102.0)	4.17(102.4)	-26.6	-1.07	4.06(99.2)	4.09(100.3)	-13.0	-0.57	4.10(100.8)	4.09(100.6)	- 8.4	-0.32	4.09(100.7)	4.26(104.7)	- 4.8	-0.19
SEM	0.31 5.0	0.30 4.9	6.8	0.27	0.30 4.0	0.31 5.2	4.8	0.20	0.29 3.8	0.31 3.5	6.0	0.23	0.34 6.3	0.31 5.4	2.3	0.10
t							2.15	2.11			3.41	4.86			3.06	3.00
P value							NS	NS			<0.02	<0.01			<0.02	<0.02
Non-responders																
9	6.09(112.7)	6.09(112.6)	-36.2	-2.20	5.46(101.1)	6.49(120.1)	- 0.8	-0.05	5.98(110.7)	6.88(127.4)	-40.2	-2.76	5.08(94.0)	6.62(122.5)	- 4.9	-0.32
10	4.16(104.0)	4.33(108.2)	-37.9	-1.64	4.40(110.0)	4.20(105.0)	+ 0.0	+0.00	4.43(110.7)	4.43(110.7)	-21.3	-0.94	4.43(110.7)	4.42(110.7)	+ 0.2	+0.01
11	5.09(138.3)	5.09(138.3)	-15.0	-0.76	4.72(128.2)	4.84(131.5)	+ 0.6	+0.03	4.62(125.5)	4.82(130.9)	- 4.2	-0.20	4.84(131.5)	4.98(135.3)	+ 2.8	+0.10
12	3.41(77.8)	3.55(81.0)	-29.3	-1.04	3.11(71.0)	3.28(74.8)	- 9.8	-0.32	3.12(71.2)	3.83(87.4)	-33.0	-1.26	3.50(79.9)	3.75(85.6)	- 3.2	-0.12
13	3.83(90.1)	3.73(87.7)	-30.3	-1.13	3.53(83.0)	3.70(87.0)	-27.9	-1.03	3.65(85.8)	3.83(90.1)	-20.2	-0.77	3.41(80.2)	3.58(84.2)	-14.6	-0.52
Mean	4.51(104.5)	4.55(105.5)	-29.8	1.35	4.24(98.6)	4.46(103.6)	- 7.6	-0.27	4.34(100.7)	4.71(109.3)	-23.8	-1.18	4.27(99.2)	4.63(107.6)	- 4.0	-0.17
SEM	0.48 10.3	0.46 10.1	4.0	0.25	0.41 10.0	0.56 10.3	5.4	0.19	0.48 9.7	0.56 9.0	6.1	0.42	0.34 9.8	0.54 10.0	2.9	0.11
t							3.37	2.97			1.43	0.70			6.19	4.83
P value							<0.05	<0.05			NS	NS			<0.01	<0.01

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

B, before pre-treatment; A, after saline, sodium cromoglycate, ipratropium bromide or ipratropium bromide plus sodium cromoglycate

Percentage and absolute fall in FVC after exercise are calculated from baseline (A)

P values refer to the difference between results after control exercise and those after sodium cromoglycate or ipratropium bromide or ipratropium bromode plus sodium cromoglycate

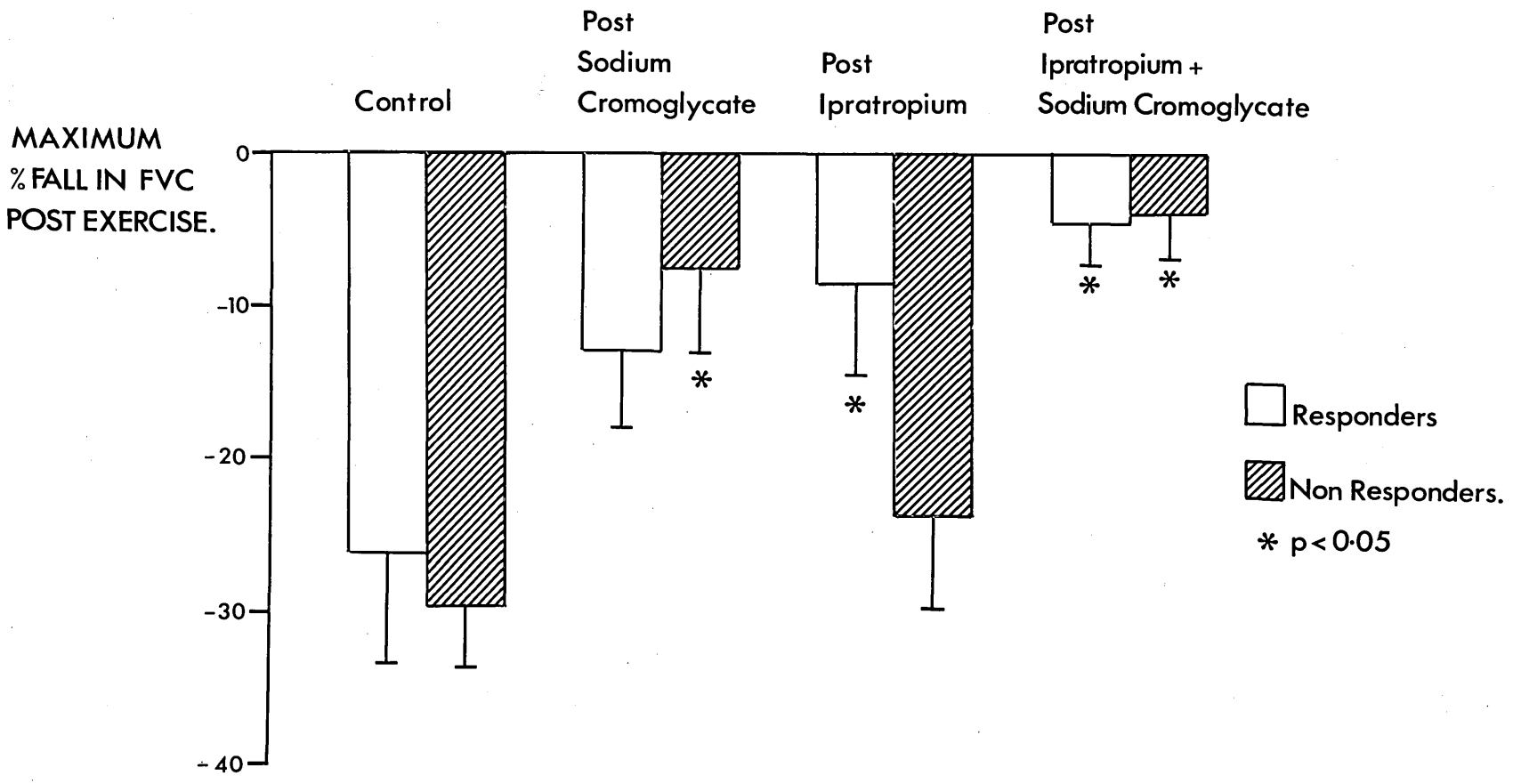

FIGURE 25 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FVC AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING SODIUM CROMOGLYCATE, IPRATROPIUM, IPRATROPIUM PLUS SODIUM CROMOGLYCATE OR SALINE IN RESPONDERS (N = 8) AND NON-RESPONDERS (N = 5)

TABLE XXVIII Maximum fall in MMEF after exercise following sodium cromoglycate, ipratropium bromide or ipratropium bromide plus sodium cromoglycate

Patient No	CONTROL Baseline B	CONTROL Baseline A	CONTROL % fall	CONTROL Absolute fall (l)	SODIUM CROMOGLYCATE Baseline B	SODIUM CROMOGLYCATE Baseline A	SODIUM CROMOGLYCATE % fall	SODIUM CROMOGLYCATE Absolute fall (l)	IPRATROPIUM BROMIDE Baseline B	IPRATROPIUM BROMIDE Baseline A	IPRATROPIUM BROMIDE % fall	IPRATROPIUM BROMIDE Absolute fall (l)	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Baseline B	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Baseline A	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE % fall	IPRATROPIUM BROMIDE + SODIUM CROMOGLYCATE Absolute fall (l)
Responders																
1	2.43(55.2)	2.51(57.0)	-45.9	-1.10	2.63(59.7)	2.21(50.2)	-34.2	-0.71	1.90(43.1)	3.33(75.6)	-47.5	-1.58	2.49(56.5)	3.80(86.3)	-34.8	-1.32
2	2.02(42.0)	2.12(44.1)	-50.0	-1.06	1.75(36.4)	2.41(50.2)	+16.5	+0.40	2.55(53.1)	3.42(71.2)	-49.8	-1.70	2.23(46.4)	3.50(72.9)	-31.8	-1.01
3	2.16(48.0)	2.46(54.6)	-34.2	-0.84	2.71(60.2)	3.09(68.6)	-28.2	-0.87	2.48(55.1)	3.16(70.2)	-23.2	-0.73	2.41(53.5)	3.95(87.7)	-25.1	-0.81
4	3.06(56.6)	2.47(45.7)	-68.1	-1.68	1.72(31.8)	1.87(34.6)	-26.8	-0.50	2.66(49.2)	4.07(75.3)	-21.7	-0.88	1.90(35.1)	3.68(68.1)	- 6.6	-0.24
5	5.21(81.4)	4.75(74.2)	-47.4	-2.25	5.05(78.9)	5.16(80.6)	- 9.2	-0.46	4.47(69.8)	5.49(85.7)	-34.3	-1.88	5.06(79.0)	5.38(84.0)	+ 4.8	+0.26
6	3.32(69.1)	3.56(74.1)	-29.8	-1.06	3.24(67.5)	3.89(81.0)	- 6.2	-0.24	4.23(88.1)	3.79(78.9)	-13.5	-0.51	3.54(73.7)	3.79(78.9)	- 5.3	-0.20
7	2.58(44.4)	2.63(51.8)	-54.0	-1.42	2.53(43.6)	3.15(54.3)	-52.1	-1.64	3.01(51.8)	3.04(52.4)	-60.9	-1.85	2.38(41.0)	2.98(51.3)	-64.1	-1.91
8	1.91(40.6)	2.33(49.5)	-78.6	-1.83	2.03(43.1)	2.95(62.7)	-64.1	-1.89	1.65(35.1)	2.79(59.3)	-72.1	-1.92	2.64(56.1)	3.24(68.9)	-23.2	-0.75
Mean	2.83(54.6)	2.85(56.3)	-50.8	-1.40	2.70(52.6)	3.04(60.2)	-25.8	-0.73	2.81(55.6)	3.59(71.0)	-40.4	-1.38	2.78(55.1)	3.77(74.7)	-23.4	-0.78
SEM	0.38 5.0	0.30 4.1	5.7	0.17	0.38 5.8	0.36 5.6	9.1	0.26	0.35 5.8	0.30 3.7	7.2	0.20	0.35 5.3	0.25 4.3	7.6	0.24
t							3.30	2.48			1.82	1.28			3.04	1.84
P value							<0.02	<0.05			NS	NS			<0.02	NS
Non-responders																
9	1.37(23.6)	1.44(24.6)	-36.9	-0.53	1.79(30.8)	1.90(36.2)	- 3.4	-0.13	1.51(26.0)	2.20(39.6)	-42.2	-1.33	1.18(20.3)	2.28(41.0)	-20.2	-0.46
10	2.95(64.1)	2.63(57.1)	-70.8	-1.86	2.42(52.6)	2.00(43.4)	- 2.5	-0.05	2.03(46.3)	2.13(48.4)	-57.4	-1.18	2.48(56.0)	3.26(73.0)	- 9.0	-0.20
11	3.23(59.8)	2.97(55.0)	-48.5	-1.44	2.66(49.2)	2.50(48.1)	-12.4	-0.22	1.78(32.9)	3.16(58.5)	-42.5	-1.34	2.83(52.4)	3.53(65.3)	-11.7	-0.41
12	0.78(13.9)	0.85(15.1)	-18.9	-0.16	0.72(12.8)	0.71(12.6)	- 1.5	-0.01	0.72(12.8)	0.78(13.9)	-33.4	-0.26	0.97(17.3)	1.17(20.8)	+11.9	+0.07
13	0.75(12.7)	0.78(25.2)	-36.0	-0.28	0.83(14.0)	0.86(14.5)	-34.0	-0.25	1.17(19.8)	1.12(18.9)	-50.9	-0.57	0.70(11.8)	0.85(14.4)	-34.0	-0.26
Mean	1.81(34.8)	1.73(35.4)	-42.3	-0.85	1.68(31.8)	1.50(30.9)	-10.8	-0.13	1.34(27.5)	1.74(27.5)	-49.3	-0.93	1.53(31.5)	2.09(42.9)	-14.8	-0.26
SEM	0.53 11.2	0.45 8.6	8.5	0.26	0.39 8.4	0.36 7.3	6.1	0.04	0.24 5.7	0.43 5.7	5.1	0.22	0.43 9.3	0.54 11.6	8.4	0.09
t							2.84	2.09			0.54	0.34			2.94	1.87
P value							<0.05	NS			NS	NS			<0.05	NS

Baseline data are expressed as absolute values (ls^{-1}) and percentage of predicted (brackets)

B, before pre-treatment; A, after saline, sodium cromoglycate, ipratropium bromide or ipratropium bromide plus sodium cromoglycate

Percentage and absolute fall in MMEF after exercise are calculated from baseline (A)

P values refer to the difference between results after control exercise and those after sodium cromoglycate or ipratropium bromide or ipratropium bromide plus sodium cromoglycate

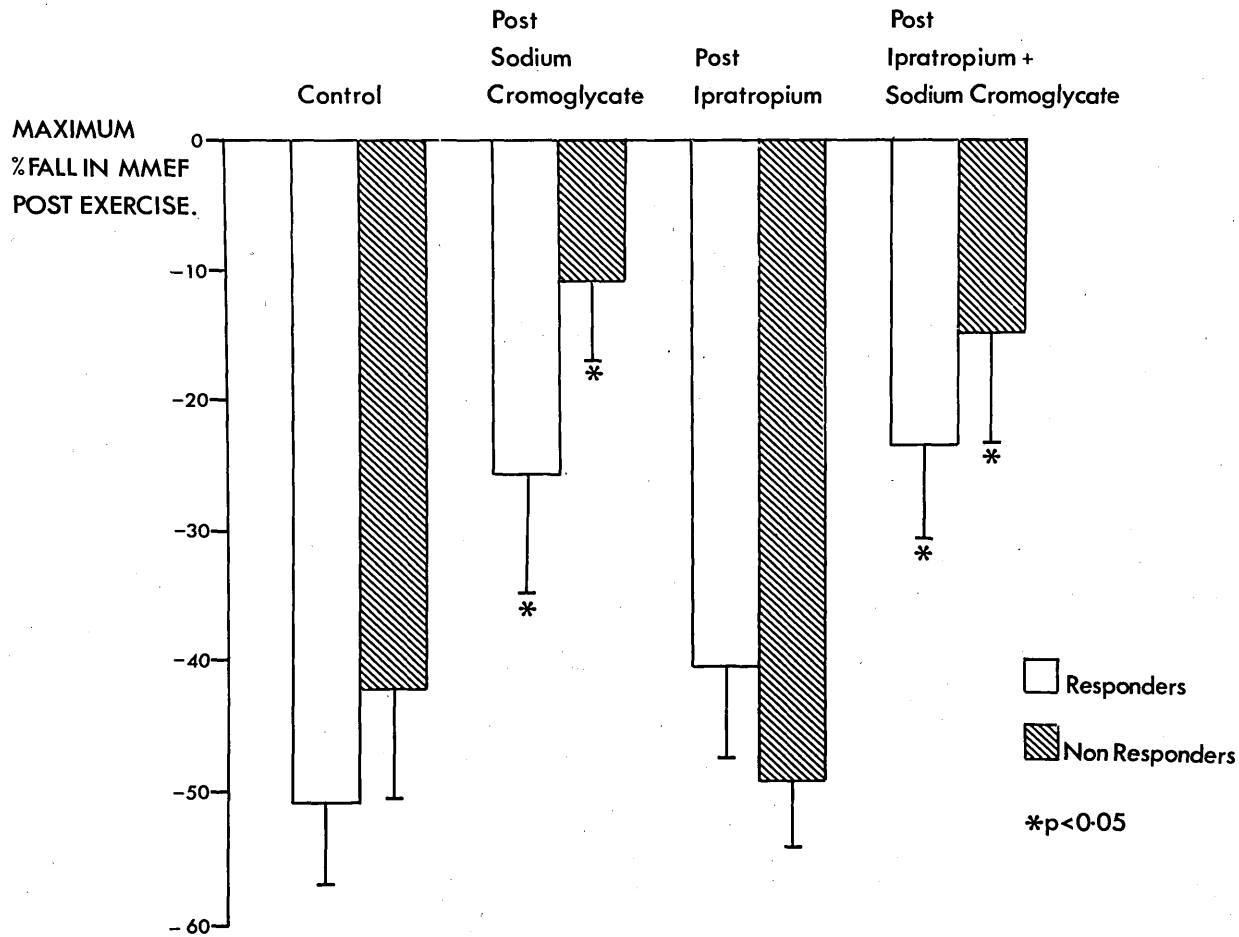

FIGURE 26 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN MMEF AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING SODIUM CROMOGLYCATE, IPRATROPIUM, IPRATROPIUM PLUS SODIUM CROMOGLYCATE OR SALINE IN RESPONDERS (N = 8) AND NON-RESPONDERS (N = 5)

DISCUSSION

Patients with asthma have been separated into two groups by measuring the MMEF rate response to low density gas breathing (Despas, Leroux & Macklem, 1972). Those showing an increase in flow rates on breathing helium are thought to have the major site of resistance to expiratory flow in the large central airways (classified responders), while in those showing no such increase, the major site is in the small peripheral airways (classified non-responders). Other factors affecting the major site of obstruction may be cigarette smoking and the presence of chronic bronchitis or recurrent respiratory infections (Antic & Macklem, 1976). Using this classification, eight patients in our study were responders while five were non-responders. The predicted baseline values of FEV_1 and FVC did not differ between the two groups. Non-responders had, however, significantly lower flow rates in small airways as assessed by baseline MMEF rates (McFadden & Linden, 1972).

In this study both SCG alone and in combination with IB inhibited EIA, as measured by fall in FEV_1, in both responders and non-responders, while IB had a preventive action only in responders. IB had no inhibitory activity, however, in either responders or non-responders when assessed by the change in MMEF, while SCG was significantly inhibitory in both these groups. If MMEF is a test of small airways calibre (McFadden & Linden, 1972) then IB unlike SCG would appear

to have no inhibitory action on these airways. In both responders and non-responders there was no difference in the effectiveness of the drugs shown to have a preventive action in EIA. SCG, although given in nebulised form which is likely to have increased its penetration into the lungs, was given in the dose normally used from a spinhaler. The present result, therefore, confirms its effect in EIA reported by others (Davies, 1968; Godfrey & Kŏnig, 1976). The estimated dose of IB nebulised was 2.0 mg which is 50 times the normal therapeutic dose. Higher doses of anticholinergic agents are probably no more effective in preventing EIA (Chapter VI). In previous studies comparing SCG and IB in extrinsic asthmatics, Chan-Yeung (1977) reported the prevention of EIA in three out of four patients by IB and all by SCG, while Godfrey & Kŏnig (1976) prevented EIA in three out of seven patients with atropine methonitrate and six out of seven with SCG. These authors did not, however, identify any differences between their patients and the therapeutic responses observed.

McFadden et al, (1977[b]) studied 12 patients with EIA who were all responders prior to exercise. IB inhibited those in whom density dependence increased after exercise indicating predominantly large airways obstruction but had no effect in those with predominantly small airways obstruction as assessed by a decrease in density dependence. This latter group, however, showed diminution in EIA by the addition of SCG. Despite not giving SCG alone, they proposed that

mediator release might serve to initiate reflex bronchoconstriction. In our study, post exercise density dependence was measured in two responders, one showing an increase and the other a decrease in the density dependence. The response to IB in these two patients was similar to that predicted by McFadden et al, (1977[b]). The non-responder prior to exercise remained so after exercise as has been found by others (Chan Yeung et al, 1976).

The results of this study are in keeping with IB acting mainly in the large airways and SCG acting in both small and large airways. In addition, SCG by nebuliser appears to be equally effective in both responders and non-responders. The relevance of these findings in relation to the pathogenesis of EIA depends on the mode of action of SCG and IB. SCG is thought to act by temporarily stabilizing the mast cell and so preventing mediator release (Orr et al, 1970). More recently, using a canine model of reflex bronchoconstriction, Jackson & Richards (1977) suggested that SCG may also reduce the activity of lung irritant receptors. This latter mode of action has not, however, been demonstrated in humans (Chapter V). IB could act on mast cells preventing mediator release (Kaliner, Orange & Austen, 1972) although this seems unlikely since SCG was effective in patients in whom IB was not. IB could also be acting directly on smooth muscle cholinergic receptors which might implicate reflex vagal bronchoconstriction, or direct cholinergic stimulation.

In addition, the bronchodilation from IB might result in reduced bronchial reactivity, due to a change in baseline airflow obstruction (Benson, 1975), although in this study an increase in airways calibre following IB occurred in both responders and non-responders. A possible interpretation of the findings in this study is that mediator release is important in most extrinsic asthmatics with EIA. In those in whom the main site of airflow obstruction is in the large central airways, which are predominantly under vagal control, mediator release results in bronchoconstriction due to cholinergic mechanisms and direct smooth muscle action. When the main site of airflow obstruction is in the smaller airways under lesser vagal control, mediator release causes bronchoconstriction due to its direct action on smooth muscle, cholinergic activity being of little importance to overall airways calibre. In support of this hypothesis, the vagus nerve predominantly effects bronchomotor tone in the large airways (Vincent et al, 1970; Simonsson, 1972) and atropine has proportionally greater activity in these airways (Cavenaugh & Cooper, 1976; Ingram et al, 1977). Unfortunately the bronchoconstrictor action of the local anaesthetic bupivacaine in asthmatics (Chapter V) prevented its use in further defining the vagal component of EIA. It would appear, however, that this proposed mechanism may not be relevant in all patients, as two patients in this study were not inhibited by any of the drugs used.

CHAPTER VIII

EFFECT OF AN ORAL CHROMONE FPL57787 IN PREVENTION OF EXERCISE-INDUCED ASTHMA

INTRODUCTION

Inhaled sodium cromoglycate prevents exercise-induced asthma (EIA) (Davies, 1968), but is inactive after oral administration due to poor gastrointestinal absorption. A new oral chromone, FPL57787, has anti-allergic activity similar to that of sodium cromoglycate (Augstein et al, 1977) and is also well absorbed from the gut.

The purpose of this study was to investigate the effect of oral FPL57787 in preventing EIA.

METHODS

Ten patients with extrinsic asthma were studied (Table XXIX). FEV_1, FVC and MMEF were measured in triplicate using a water-sealed spirometer (Godart), the best recording being used for analysis. Predicted normal values were taken from Cotes (1975) for FEV_1 and FVC and from Cherniak & Raber (1972) for MMEF. Exercises were performed on an inclined treadmill. The two exercise tests performed on each patient were completed within 10 days.

The preparations were given as eight tablets (FPL57787 12 mg and placebo) in a cachet to preserve blindness and the order of treatment was randomly assigned to each patient. Each cachet was taken with a draught of water on an empty stomach i.e. at least 30 min before a meal and not less than four hours after a previous meal. Lung function measurements

TABLE XXIX Clinical details of asthmatic patients

Patient No	Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean Baseline FEV_1 (l)	% Predicted FEV_1
1 D.McI.	24	M	171	79	4.62	115.5
2 W.W.	18	M	174	84	3.65	88.5
3 M.McN.	17	F	168	63	2.54	78.1
4 A.S.	25	M	190	80	4.00	85.1
5 V.D.	25	F	159	62	2.59	84.9
6 M.J.	17	F	162	57	3.55	113.7
7 J.A.	28	F	154	56	3.19	113.1
8 A.D.	33	F	163	73	2.76	95.1
9 R.S.	23	M	175	81	4.60	110.8
10 A.B.	36	F	157	68	1.79	66.7

were made pre-treatment, two hours post-treatment i.e. immediately before exercise and at 2, 5, 10, 15 and 20 min after the exercise had been completed. Results were expressed as the maximum percentage and absolute fall in lung function after exercise compared to the two hours post-treatment value.

Statistical analysis was performed using "Student's" paired t test.

RESULTS

The results of the tests are given in Tables XXX, XXI, XXXII, and Figures 27, 28, 29. No significant difference in pre- or two hour post-treatment values of FEV_1, FVC and MMEF was seen between the two study days. FPL57787 gave significant protection ($P < 0.01$) compared to placebo from the maximum percentage fall and maximum absolute fall in FEV_1, FVC and MMEF after exercise. Following FPL57787, seven out of ten patients had less than a 20% fall in FEV_1 after exercise, whereas following placebo all patients had greater than a 20% fall in FEV_1 after exercise.

When compared to placebo, FPL57787 produced a small but significant percentage increase in FEV_1 two hour after the drug ($P < 0.01$): (mean $\pm$ ISD) Post FPL57787 10.0 ± 10.8; post placebo 2.6 ± 7.7. No significant increase was seen in FVC (post FPL57787 2.1 ± 5.6; post placebo 1.3 ± 3.7) or in MMEF (post FPL57787 16.3 ± 23.5; post placebo 15.6 ± 18.9).

TABLE XXX Maximum fall in FEV_1 after exercise following FPL57787 or placebo

Patient No	PLACEBO Baseline B	PLACEBO Baseline A	PLACEBO %fall	PLACEBO Absolute fall (l)	FPL57787 (12 mg) Baseline B	FPL57787 (12 mg) Baseline A	FPL57787 (12 mg) %fall	FPL57787 (12 mg) Absolute fall (l)
1	4,45(111.2)	4.35(108.7)	-29.9	-1.30	4.79(119.7)	5.02(125.5)	- 4.6	-0.23
2	3.72(90.2)	3.85(93.4)	-55.6	-2.14	3.58(86.8)	4.05(98.3)	-30.6	-1.24
3	2.85(87.6)	2.56(78.7)	-23.0	-0.59	2.24(68.9)	2.31(71.0)	-17.3	-0.40
4	3.85(81.9)	4.49(95.5)	-59.5	-2.67	4.15(88.2)	5.05(107.4)	-40.4	-2.04
5	2.81(92.1)	3.08(100.9)	-46.8	-1.44	2.38(78.0)	3.03(99.3)	-17.2	-0.52
6	3.48(111.5)	3.28(105.1)	-26.5	-0.87	3.63(116.3)	3.55(113.7)	-10.4	-0.37
7	2.98(105.6)	2.91(103.6)	-31.6	-0.92	2.90(102.8)	2.85(101.0)	-16.1	-0.46
8	2.58(88.9)	2.58(89.9)	-40.3	-1.04	2.95(101.7)	2.95(101.7)	-17.2	-0.51
9	4.85(116.8)	5.10(122.8)	-56.0	-2.86	4.35(104.8)	4.97(119.2)	-35.4	-1.76
10	1.76(65.6)	1.84(68.6)	-48.9	-0.90	1.82(67.9)	2.28(85.0)	-17.9	-0.41
Mean	3.33(95.1)	3.40(96.7)	-41.8	-1.47	3.28(93.5)	3.61(102.2)	-20.7	-0.79
SEM	0.29 5.03	0.32 4.87	4.2	0.25	0.31 5.83	0.35 5.03	3.5	0.20
t							8.91	7.13
P value							<0.01	<0.01

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

B, before pre-treatment; A, after placebo or FPL57787

Percentage and absolute fall in FEV_1 after exercise are calculated from baseline (A)

P values refer to the difference between results after placebo and those after FPL57787

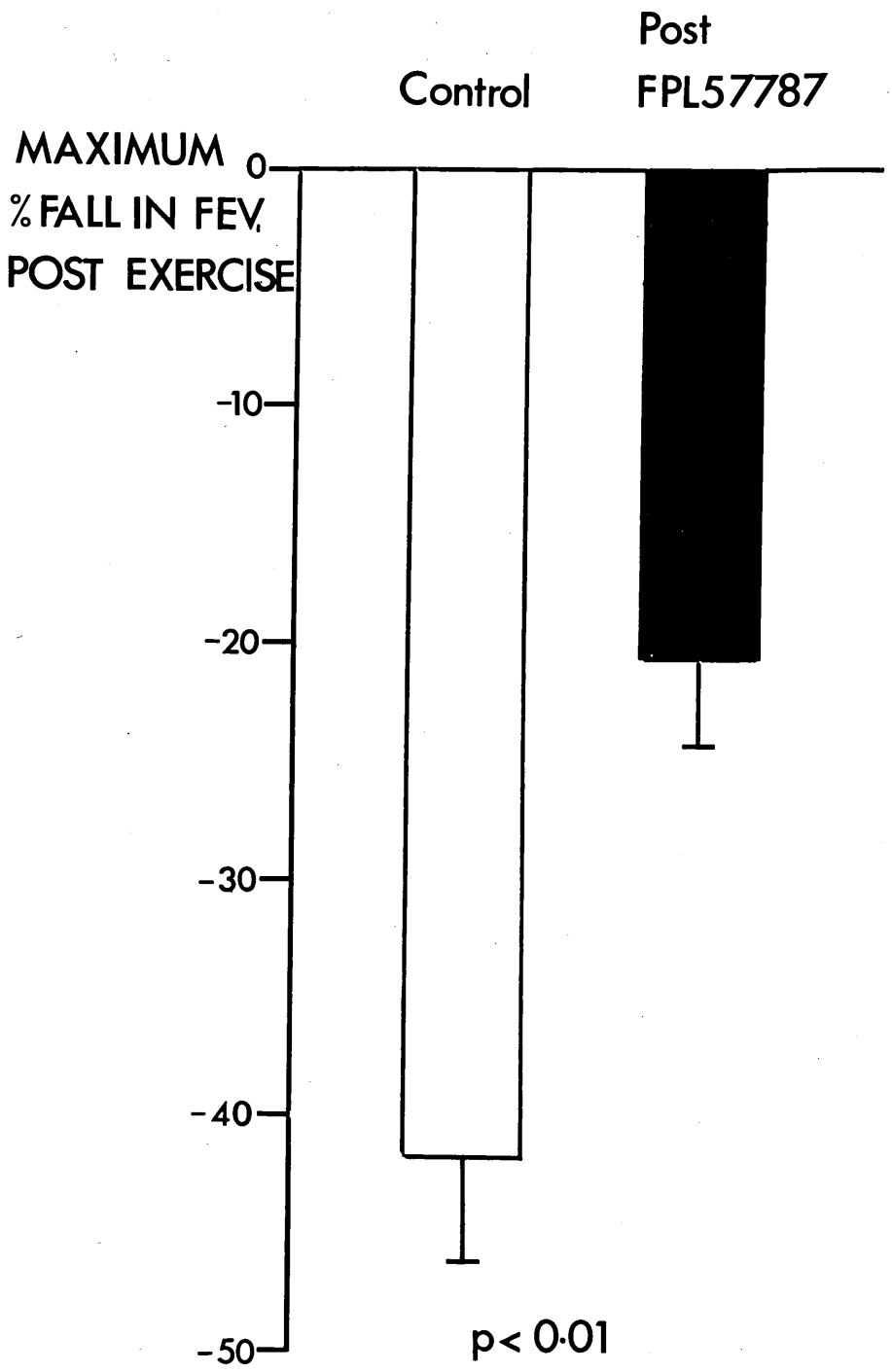

FIGURE 27 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FEV_1 AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING FPL57787 OR PLACEBO IN ASTHMATIC PATIENTS (N = 10)

TABLE XXXI Maximum fall in FVC after exercise following FPL57787 or placebo

Patient No	PLACEBO Baseline B	A	%fall	Absolute fall (l)	FPL57787 (12 mg) Baseline B	A	%fall	Absolute fall (l)
1	5.36(112.8)	5.29(111.3)	-10.2	-0.54	5.56(117.0)	5.52(116.2)	- 0.0	-0.00
2	5.29(107.9)	5.59(114.0)	-40.8	-2.28	5.35(109.0)	5.62(114.6)	-14.2	-0.80
3	4.02(101.7)	3.88(98.2)	- 6.7	-0.26	3.95(100.0)	3.62(91.6)	- 3.9	-0.14
4	6.89(120.8)	7.00(122.8)	-42.6	-2.98	6.89(120.8)	7.36(129.1)	-16.7	-1.23
5	4.07(114.6)	4.44(125.0)	-30.6	-1.36	3.93(110.7)	4.39(123.6)	- 7.7	-0.34
6	4.52(123.8)	4.69(128.4)	-10.0	-0.47	4.79(131.2)	4.65(127.3)	+ 1.9	+0.09
7	3.38(102.4)	3.41(103.3)	-18.4	-0.63	3.36(98.2)	3.45(104.5)	- 5.7	-0.20
8	3.35(95.7)	3.30(94.2)	-20.9	-0.69	3.65(104.2)	3.72(106.2)	-16.3	-0.61
9	5.69(114.9)	5.76(116.3)	-30.2	-1.74	5.62(113.5)	5.59(129.2)	-12.8	-0.72
10	3.65(114.0)	3.58(111.8)	-27.3	-0.98	3.62(113.1)	3.82(119.2)	- 8.1	-0.31
Mean	4.62(110.8)	4.69(112.5)	-23.7	-1.19	4.67(111.7)	4.77(116.1)	- 8.3	-0.43
SEM	0.37 2.79	0.38 3.58	4.0	0.28	0.36 3.12	0.39 3.89	2.0	0.12
t							5.82	4.42
P value							<0.01	<0.01

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

B, before pre-treatment; A, after placebo or FPL57787

Percentage and absolute fall in FVC after exercise are calculated from baseline (A)

P values refer to the difference between results after placebo and those after FPL57787

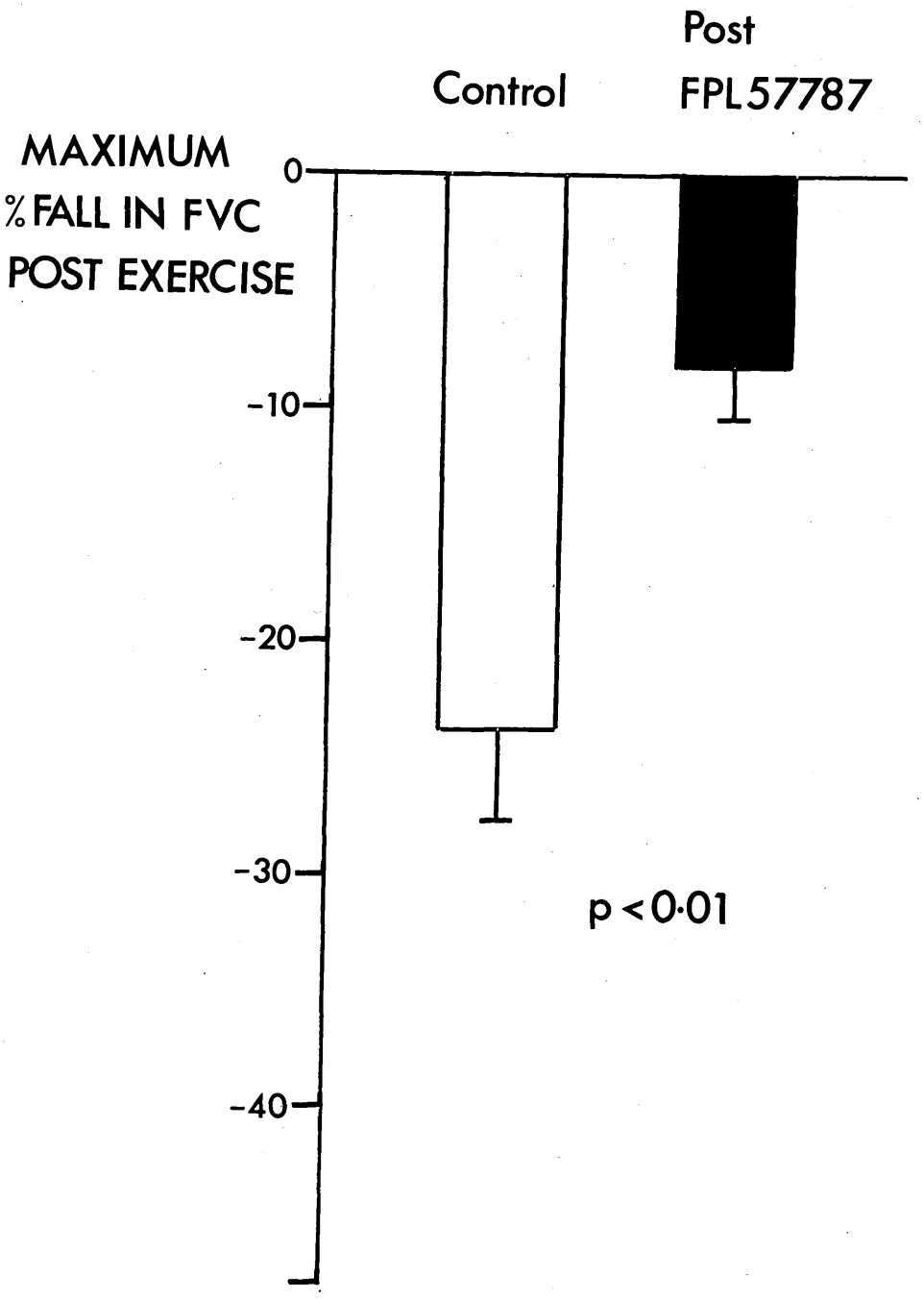

FIGURE 28 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FVC AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING FPL57787 OR PLACEBO IN ASTHMATIC PATIENTS (N = 10)

TABLE XXXII Maximum fall in MMEF after exercise following FPL57787 or placebo

Patient No	PLACEBO Baseline B	A	%fall	Absolute fall (l)	FPL57787 (12 mg) Baseline B	A	%fall	Absolute fall (l)
1	4.81(82.9)	5.04(86.8)	-66.3	-3.34	5.85(100.8)	7.32(126.2)	-24.0	-1.76
2	2.64(43.2)	2.68(43.9)	-66.4	-1.78	2.68(43.9)	2.96(48.5)	-50.0	-1.48
3	2.06(40.3)	1.81(35.4)	-45.9	-0.83	1.24(24.3)	1.51(29.3)	-35.1	-0.53
4	1.89(30.4)	2.59(41.7)	-66.4	-1.72	2.37(38.2)	3.27(52.7)	-64.2	-2.10
5	1.87(40.6)	2.19(47.6)	-58.4	-1.28	1.36(29.5)	2.08(45.2)	-31.3	-0.65
6	2.85(59.3)	2.39(49.7)	-37.7	-0.90	2.92(60.5)	3.00(62.5)	-24.7	-0.74
7	3.72(86.5)	3.79(88.1)	-66.2	-2.51	3.38(78.6)	2.79(64.8)	-32.9	-0.92
8	2.57(58.4)	2.38(54.0)	-64.7	-1.54	3.07(69.7)	3.09(70.2)	-29.7	-0.95
9	4.94(82.3)	6.10(101.6)	-78.6	-4.80	5.66(94.3)	5.62(93.6)	-58.1	-3.27
10	0.78(18.5)	0.88(20.9)	-60.2	-0.48	0.77(18.3)	1.24(29.5)	-28.2	-0.35
Mean	2.81(54.2)	2.98(56.9)	-61.0	-1.92	2.93(55.8)	3.29(62.2)	-37.8	-1.28
SEM	0.42 7.48	0.49 8.28	3.6	0.41	0.54 9.30	0.59 9.35	4.5	0.28
t							5.79	2.93
P values							<0.01	<0.02

Baseline data are expressed as absolute values (1 sec^{-1}) and percentage of predicted (brackets)

B, before pre-treatment; A, after placebo or FPL57787

Percentage and absolute fall in MMEF after exercise are calculated from baseline (A)

P values refer to the difference between results after placebo and those after FPL57787

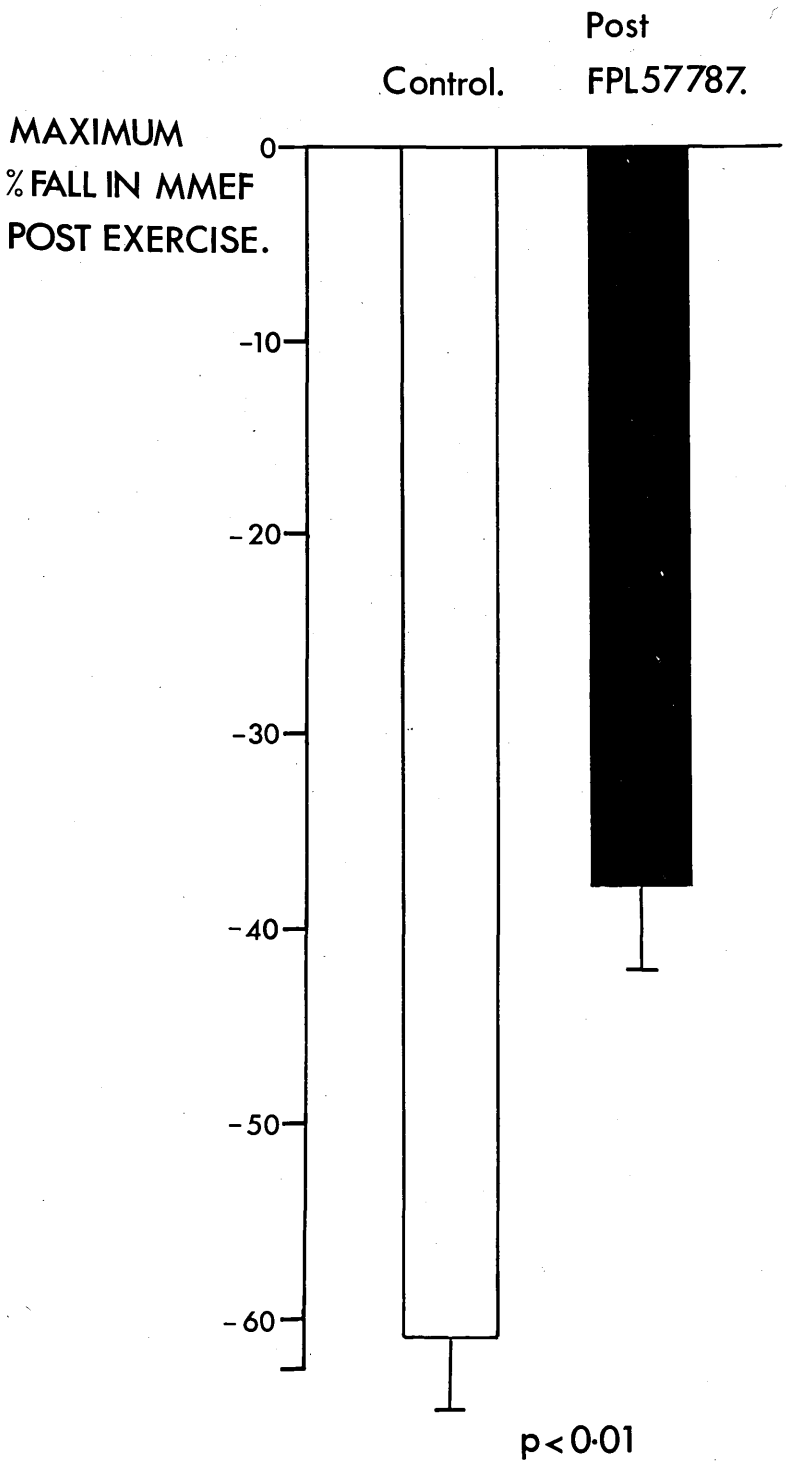

FIGURE 29 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN MMEF AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING FPL57787 OR PLACEBO IN ASTHMATIC PATIENTS (N = 10)

Detailed results for each patient are tabulated in Appendix D, Tables LXXVIII - LXXX.

DISCUSSION

Both FPL57787 and sodium cromoglycate would appear to inhibit antigen-induced release of pharmacological mediators by stabilization of mast cell membranes (Orr et al, 1970; Augstein et al, 1977). In addition, FPL57787, unlike sodium cromoglycate, may also inhibit degranulation of basophils (Augstein et al, 1977). Recently, resulting from experiments with a canine model of reflex bronchoconstriction, Jackson & Richards (1977) suggested that sodium cromoglycate may have a blocking action on lung irritant receptors. It is possible, therefore, that a derivative of sodium cromoglycate. such as FPL57787, may have similar properties. However, in humans a blocking action of sodium cromoglycate on irritant receptors has yet to be demonstrated (Chapter V). If the principal effect of FPL57787 in man is the inhibition of mast cell degranulation, then the result of this study supports the hypothesis that exercise in asthmatic patients provokes mediator release (Godfrey, 1975; Chapter VII). The small improvement in pre-exercise lung function after FPL57787 compared to after placebo is unlikely to have been sufficient to account for its protective action, since the two hour post-treatment values of FEV_1, FVC and MMEF between the two study days were not significantly different. The apparent slight bronchodilation produced by FPL57787 in this study is

unexplained, but was also noted in a pilot study on four asthmatic patients given 24 mg of FPL57787.

A drug shown to be effective in preventing exercise-induced asthma in the laboratory may not be clinically useful. The effectiveness of FPL57787 in the long term prophylaxis of asthma is under study.

CHAPTER IX

EFFECT OF H_1 RECEPTOR AND H_2 RECEPTOR ANTAGONISTS IN PREVENTION OF EXERCISE-INDUCED ASTHMA

INTRODUCTION

Mediators of immediate hypersensitivity including histamine are released when sensitized human lung tissue interacts with specific antigen *in vitro* (Austen & Orange, 1975). It has been suggested that exercise challenge in asthmatics may also provoke mediator release (Godfrey, 1975). This hypothesis is supported by the finding that sodium cromoglycate and FPL57787, which inhibit the release of type I mediators from mast cells (Orr *et al*, 1970; Augstein *et al*, 1977), may prevent exercise-induced asthma (EIA) through a similar mechanism (Davies, 1968; Godfrey & König, 1968; McFadden *et al*, 1977[b]; Chapters VII and VIII). In addition, raised arterial plasma histamine levels have been found after exercise in some studies (Ferris *et al*, 1978) although this has not been confirmed by others (Harries, O'Brien & Burge, 1979).

The purpose of this study was to investigate the effects of H_1 and H_2 receptor antagonists in the prevention of EIA. It was hoped that this might help define the role, if any, of histamine in EIA.

METHODS

Ten patients with extrinsic asthma were studied (Table XXXIII). FEV_1, FVC and MMEF were measured in triplicate using a water-sealed spirometer (Godart), the best recording being used for analysis. Predicted

TABLE XXXIII Clinical details of asthmatic patients

Patient No		Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean Baseline FEV_1 (l)	% Predicted FEV_1
1	D.D.	45	M	177	85	3.77	100.5
2	N.B.	24	M	183	76	5.44	120.8
3	L.R.	29	F	159	48	2.23	75.5
4	C.N.	20	F	155	67	2.75	93.2
5	R.G.	32	F	158	52	2.92	103.5
6	M.S.	18	M	171	73	3.55	88.7
7	P.H.	30	F	165	50	2.85	93.4
8	M.S.	24	M	164	73	2.89	78.1
9	M.P.	33	F	167	51	2.83	94.3
10	C.G.	21	F	149	50	1.99	72.3

normal values were taken from Cotes (1975) for FEV_1 and FVC and from Cherniak and Raber (1972) for MMEF. Exercises were performed on an inclined treadmill. The three exercise tests performed on each patient were all completed within 10 days.

The studies were carried out in a random double-blind fashion using the following agents administered by a Wright nebuliser during 5 min tidal breathing: (1) clemastine (0.5 g/l, 1.0 mmol/l) - estimated dose nebulised 0.5 mg; (2) cimetidine (100 g/l, 0.39 mol/l) - estimated dose nebulised 100 mg; (3) saline solution (9 g/l, 0.15 mol/l). Following baseline measurements of FEV_1, FVC and MMEF, the drug solution was inhaled for 5 min. After 30 min spirometry was repeated, and then at 2, 5, 10, 15 and 20 min after the exercise test. A positive response was defined as one in which there was a decrease in FEV_1 of more than 20%. Results of exercise tests were expressed as the maximum percentage and absolute fall in lung function after exercise compared to the post-drug or placebo baseline. Statistical analysis was performed using "Student's" paired t test.

RESULTS

The results of the tests are given in Tables XXXIV, XXXV, XXXVI and Figures 30, 31, 32. No significant difference in pre- or 30 min post-treatment values of FEV_1, FVC and MMEF was seen between the three

study days. Cimetidine but not clemastine gave significant protection ($P < 0.01$) compared to placebo from the maximum percentage fall and maximum absolute fall in FEV_1 and MMEF after exercise. There was no significant difference in values of FEV_1, FVC and MMEF after exercise following pre-treatment with clemastine or cimetidine. No side effects were noted after either clemastine or cimetidine.

Detailed results for each patient are tabulated in Appendix D, Tables LXXXI - LXXXIX.

DISCUSSION

Bronchial lumen mast cells have been demonstrated in animals (Patterson et al, 1974) and man (Patterson et al, 1977; Ts'ao et al, 1977), and transfer of these cells from rhesus monkeys with airway reactivity to ascaris antigen has been reported to result in transient airway reactivity in recipient animals (Patterson et al, 1978). Furthermore, sensitized mast cells have been shown to release mediators by non-immunological mechanisms (Vane, 1971; Seale & Piper, 1978). It has been suggested, therefore, that in patients with asthma exercise may provoke chemical mediator release from sensitized mast cells (Godfrey, 1975), possibly as a result of airways cooling during exercise (McFadden & Ingram, 1979).

The reduction in the immediate bronchial response to inhaled antigen following pre-treatment with H_1

antagonists (Nakazawa et al, 1976; Eiser et al, 1978[b]) and the finding of raised histamine levels after antigen-induced bronchoconstriction (Bhat et al, 1977) suggests that histamine may be one of the chemical mediators released from mast cells following antigen challenge. The effect of H_1 receptor antagonists in EIA has previously been examined in a few patients. No significant protection against EIA was found with parenteral mepyramine maleate (50 mg) in 5 asthmatics (McNeill et al, 1966), or with oral chorpheniramine (4 mg) in 2 asthmatics (Bianco et al, 1974). The present results confirm these observations in a larger number of patients studied in a double-blind fashion. The failure of the H_1 receptor antagonist clemastine to inhibit EIA may be due to a number of factors. The dose of clemastine might have been insufficient to block local tissue levels of released histamine following exercise, although the dose of clemastine used in this study has been previously shown to reduce histamine induced bronchoconstriction in asthmatics (Chapter III). In addition, the deposition of the aerosol of clemastine to the H_1 receptors in the smaller airways, and hence the degree of H_1 receptor blockade may have been much less than in the larger central airways. If, however, the dose and method of administration of clemastine was sufficient to produce adequate H_1 receptor blockade, then these results suggest that either the release of chemical mediators from mast cells is not important in the pathogenesis of EIA or a mediator other than

histamine such as SRS-A is of more relevance. The main evidence for chemical mediator release from mast cells occurring following EIA is dependent upon the inhibitory action of sodium cromoglycate (Davies, 1968; Chapter VII) and FPL57787 (Chapter VIII) in EIA being due to these drugs reducing the release of pharmacological mediators by the stabilization of mast cell membranes (Orr et al, 1970; Augstein et al, 1977). Other postulated modes of action of sodium cromoglycate (and FPL57787) have yet to be demonstrated in man, and this has already been discussed (Chapters V, VII, VIII). Thus if these drugs action in EIA indicates mediator release, then another mediator such as SRS-A may be more important than histamine. In support of this, diethylcarbamazine, which has been shown to inhibit release of SRS-A in the rat (Orange et al, 1968) and SRS-A and histamine from passively sensitized monkey lung tissue following antigen challenge (Ishizaka et al, 1971), has been found to protect against EIA in 15 out of 20 asthmatic children (Sly & Matzen, 1974).

The main site of action of histamine on the airways of asthmatics is probably by a direct effect on bronchial smooth muscle H_1 receptors, rather than H_2 receptors (Chapter III). The partial reduction in EIA with cimetidine, at a dose and by a method of administration which has been shown to have no effect on histamine induced bronchoconstriction, suggests that cimetidine may be preventing EIA by a mode of

action other than by blocking H_2 receptors. H_2 receptor antagonists induce catecholamine release (Owen, 1977), inhibit the metabolism of histamine (Thomas, Bochner & Lichtenstein, 1978) and induce histidine decarboxylase (Maudsley et al, 1973). Of these effects only the release of catecholamines would reduce immediate hypersensitivity reactions and therefore possibly be relevant to the inhibition of EIA. Whether cimetidine is acting in this manner or by some other means remains to be elucidated.

TABLE XXXIV Maximum fall in FEV_1 after exercise following clemastine, cimetidine or saline

Patient No	PLACEBO Baseline B	PLACEBO Baseline A	PLACEBO % fall	PLACEBO Absolute fall (l)	CLEMASTINE Baseline B	CLEMASTINE Baseline A	CLEMASTINE % fall	CLEMASTINE Absolute fall (l)	CIMETIDINE Baseline B	CIMETIDINE Baseline A	CIMETIDINE % fall	CIMETIDINE Absolute fall (l)
1	3.72(99.2)	3.78(100.8)	-36.2	-1.37	3.58(95.4)	3.64(97.0)	-36.5	-1.33	4.02(107.2)	3.82(101.8)	-19.8	-0.76
2	5.35(118.8)	5.29(117.5)	-23.6	-1.25	5.35(118.8)	5.51(122.0)	-24.5	-1.35	5.62(124.8)	5.84(129.7)	-13.1	-0.77
3	2.32(78.6)	2.51(85.0)	-49.4	-1.24	2.07(70.1)	2.58(87.4)	-27.5	-0.71	2.31(78.3)	2.41(81.6)	-29.0	-0.70
4	2.63(89.1)	2.53(85.7)	-43.0	-1.09	2.78(94.2)	3.08(104.4)	-24.3	-0.75	2.84(96.2)	2.78(94.2)	-28.7	-0.80
5	3.01(106.7)	3.03(107.4)	-41.5	-1.26	3.11(110.2)	3.05(108.1)	-26.8	-0.82	2.64(93.6)	2.98(105.6)	-29.1	-0.87
6	3.52(88.0)	3.38(84.5)	-24.8	-0.84	3.62(90.5)	3.35(83.7)	-16.1	-0.54	3.52(88.0)	3.45(86.2)	-22.3	-0.77
7	2.84(93.1)	3.25(106.5)	-31.0	-1.01	3.08(100.9)	3.21(105.2)	-24.2	-0.78	2.63(86.2)	2.85(93.4)	-24.9	-0.71
8	2.89(78.1)	2.88(77.8)	-30.2	-0.87	2.91(78.6)	3.25(87.8)	-22.7	-0.74	2.88(77.8)	2.48(67.0)	- 8.0	-0.20
9	2.96(98.6)	2.88(96.0)	-23.2	-0.67	2.91(97.0)	2.91(97.0)	-36.7	-1.07	2.64(88.0)	2.34(78.0)	-22.6	-0.53
10	1.76(64.0)	1.64(59.6)	-34.7	-0.57	2.31(84.0)	2.31(84.0)	-29.0	-0.67	1.92(69.8)	1.77(64.3)	-28.2	-0.50
Mean	3.10(91.4)	3.11(92.0)	-33.7	-1.01	3.17(93.9)	3.28(97.6)	-26.8	-0.87	3.10(90.9)	3.07(90.1)	-22.5	-0.66
SEM	0.30 4.9	0.30 5.3	2.8	0.08	0.28 4.5	0.27 3.9	1.9	0.08	0.33 5.0	0.35 6.1	2.2	0.06
t							2.12	1.56			4.84	5.17
P value							NS	NS			<0.01	<0.01

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

B, before pre-treatment; A, after placebo, clemastine or cimetidine

Percentage and absolute fall in FEV_1 after exercise are calculated from baseline (A)

P values refer to the difference between results after placebo and those after clemastine or cimetidine

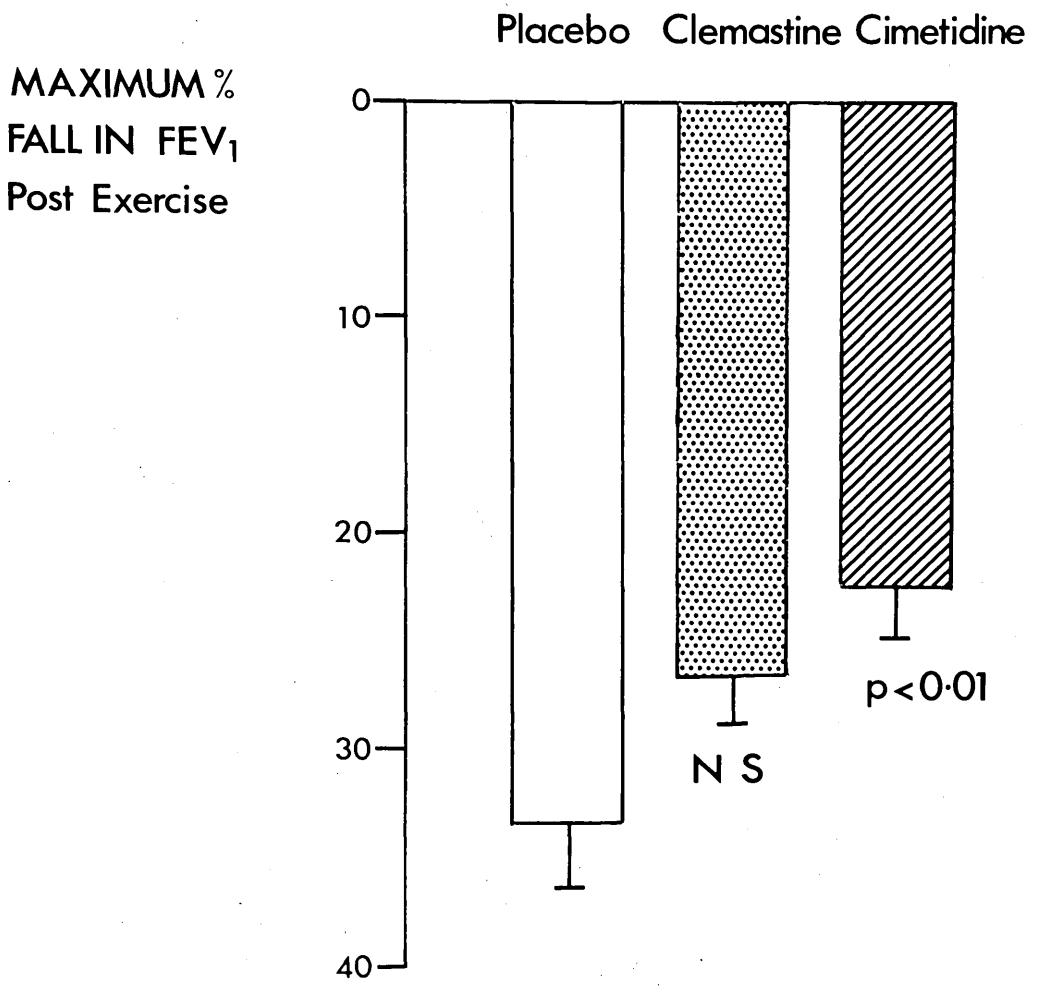

FIGURE 30 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FEV_1 AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING CLEMASTINE, CIMETIDINE OR SALINE IN ASTHMATIC PATIENTS (N = 10)

TABLE XXXV Maximum fall in FVC after exercise following clemastine, cimetidine or saline

Patient No	PLACEBO Baseline B	PLACEBO Baseline A	PLACEBO % fall	PLACEBO Absolute fall (l)	CLEMASTINE Baseline B	CLEMASTINE Baseline A	CLEMASTINE % fall	CLEMASTINE Absolute fall (l)	CIMETIDINE Baseline B	CIMETIDINE Baseline A	CIMETIDINE % fall	CIMETIDINE Absolute fall (l)
1	4.74(100.8)	4.77(101.4)	-21.3	-1.02	4.05(86.1)	4.32(91.9)	-27.3	-1.18	4.99(106.1)	4.85(103.1)	-10.9	-0.53
2	7.73(143.1)	7.61(140.9)	- 6.8	-0.52	7.78(144.0)	7.82(144.8)	- 9.8	-0.77	7.77(143.8)	7.65(141.4)	- 3.3	-0.26
3	3.21(93.0)	3.28(95.0)	-26.5	-0.87	3.20(92.7)	3.25(94.2)	-10.7	-0.35	3.28(95.0)	3.18(92.1)	-16.9	-0.54
4	3.51(106.3)	3.40(103.0)	-22.3	-0.76	3.55(107.5)	3.65(110.6)	-12.0	-0.44	3.51(106.3)	3.41(103.3)	-15.5	-0.53
5	3.68(111.5)	3.72(112.7)	-23.1	-0.86	3.77(114.2)	3.68(111.5)	- 5.9	-0.22	3.51(106.3)	3.65(110.6)	-14.2	-0.52
6	4.75(100.0)	4.25(89.4)	- 3.5	-0.15	4.57(96.2)	4.45(93.6)	- 3.8	-0.17	4.75(100.0)	4.34(91.3)	- 5.0	-0.22
7	3.95(106.7)	4.03(108.9)	-12.4	-0.50	3.75(101.3)	3.92(105.9)	-13.0	-0.51	3.88(104.8)	3.82(103.2)	-14.9	-0.57
8	4.45(101.1)	4.95(104.3)	-28.5	-1.31	4.69(106.5)	4.79(108.8)	-13.3	-0.64	4.42(100.4)	3.83(87.0)	- 1.5	-0.06
9	3.87(104.5)	3.60(97.2)	- 6.6	-0.24	3.58(96.7)	3.58(96.7)	-11.1	-0.40	3.65(98.6)	3.55(95.6)	-15.2	-0.54
10	2.81(93.6)	2.75(91.6)	-29.4	-0.81	3.11(103.6)	3.11(103.6)	-15.1	-0.47	2.81(93.6)	2.64(88.0)	-27.6	-0.73
Mean	4.27(106.0)	4.20(104.4)	-18.0	-0.70	4.20(104.8)	4.25(106.1)	-12.2	-0.51	4.25(105.4)	4.09(101.5)	-12.5	-0.45
SEM	0.43 4.4	0.42 4.6	3.0	0.11	0.42 5.0	0.42 4.8	1.9	0.09	0.44 4.5	0.43 5.0	2.4	0.06
t							1.94	1.70			1.80	1.89
P value							NS	NS			NS	NS

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)

B, before pre-treatment; A, after placebo, clemastine or cimetidine

Percentage and absolute fall in FVC after exercise are calculated from baseline (A)

P values refer to the difference between results after placebo and those after clemastine or cimetidine

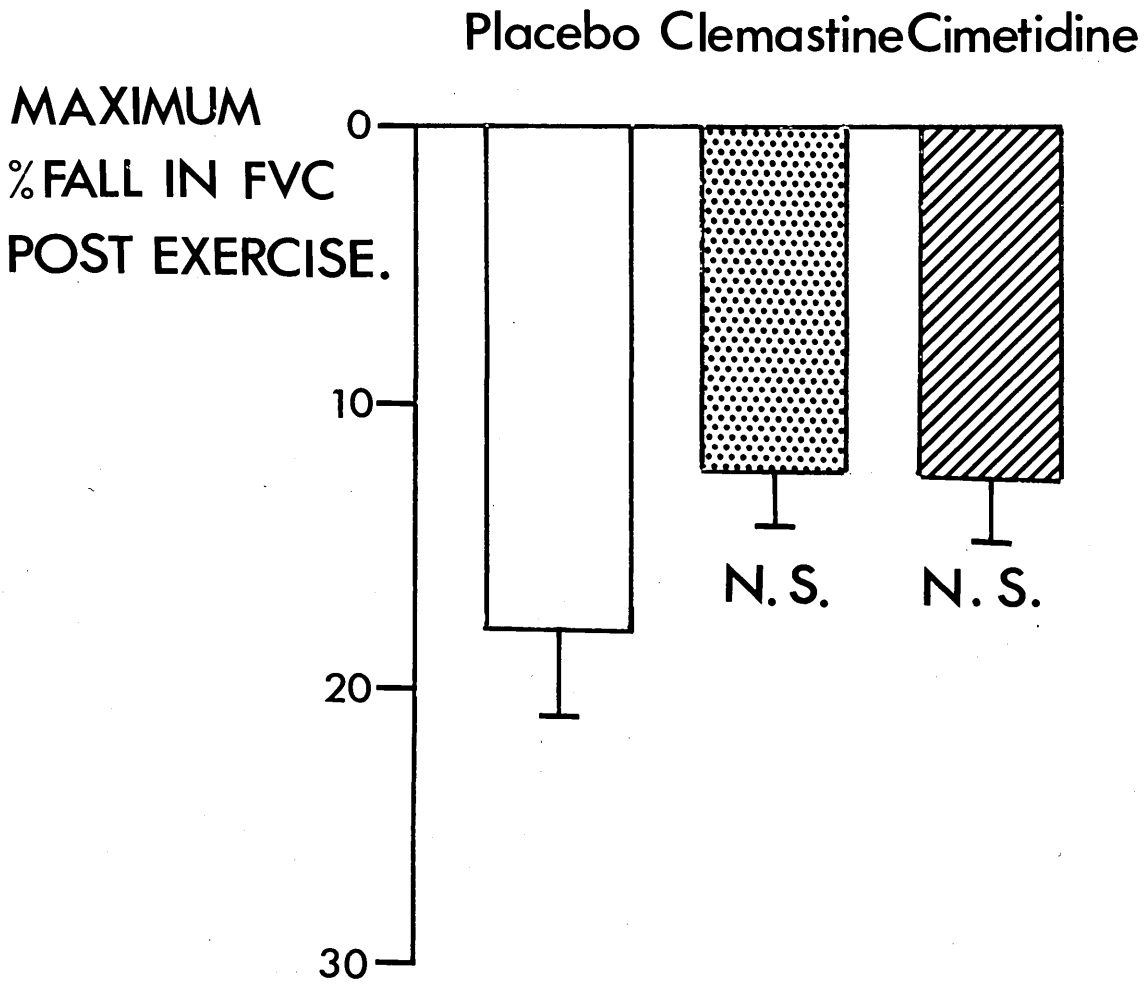

FIGURE 31 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN FVC AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING CLEMASTINE, CIMETIDINE OR SALINE IN ASTHMATIC PATIENTS (N = 10)

TABLE XXXVI Maximum fall in MMEF after exercise following clemastine, cimetidine or saline

Patient No	PLACEBO Baseline B	PLACEBO Baseline A	PLACEBO % fall	PLACEBO Absolute fall (l)	CLEMASTINE Baseline B	CLEMASTINE Baseline A	CLEMASTINE % fall	CLEMASTINE Absolute fall (l)	CIMETIDINE Baseline B	CIMETIDINE Baseline A	CIMETIDINE % fall	CIMETIDINE Absolute fall (l)
1	3.42(61.0)	3.39(60.5)	-57.2	-1.94	2.89(51.6)	3.40(60.7)	-64.7	-2.20	3.56(63.6)	3.47(61.9)	-33.7	-1.17
2	4.45(71.7)	4.63(74.6)	-39.9	-1.85	4.53(73.0)	4.71(75.9)	-36.7	-1.73	4.61(74.3)	4.65(75.0)	-27.5	-1.28
3	2.00(45.4)	2.22(50.4)	-68.0	-1.51	1.51(34.3)	2.34(53.1)	-47.4	-1.11	1.62(36.8)	1.95(44.3)	-42.0	-0.82
4	1.99(43.2)	2.01(43.6)	-65.1	-1.31	2.36(51.3)	3.47(75.4)	-31.4	-1.09	2.84(61.7)	2.53(55.0)	-44.6	-1.13
5	2.83(64.3)	2.97(67.5)	-65.5	-1.95	3.12(70.9)	3.04(69.0)	-32.5	-0.99	1.95(44.3)	2.70(61.3)	-52.9	-1.43
6	2.97(51.2)	3.01(51.8)	-41.5	-1.25	3.25(56.0)	2.60(44.8)	-31.9	-0.83	2.62(45.1)	3.08(53.1)	-37.6	-1.16
7	2.35(51.0)	3.57(77.6)	-57.9	-2.07	3.12(67.8)	3.16(68.6)	-39.8	-1.26	2.12(46.0)	2.46(53.4)	-41.4	-1.02
8	1.79(31.9)	1.79(31.9)	-37.4	-0.67	1.87(33.3)	2.16(38.5)	-36.1	-0.78	1.77(31.6)	1.56(27.8)	-19.8	-0.31
9	2.63(57.1)	2.53(55.0)	-46.2	-1.17	2.98(64.7)	2.90(29.0)	-68.6	-1.99	2.00(43.4)	1.46(31.7)	-27.3	-0.40
10	1.08(24.5)	0.87(19.7)	-37.9	-0.33	1.93(43.8)	1.89(42.9)	-57.6	-1.09	1.28(29.0)	0.88(20.0)	-39.7	-0.35
Mean	2.55(50.1)	2.69(53.2)	-51.6	-1.40	2.75(54.6)	2.96(55.7)	-44.6	-1.30	2.43(47.5)	2.47(48.3)	-36.6	-0.90
SEM	0.29 4.5	0.33 5.7	3.9	0.18	0.27 4.5	0.25 5.2	4.4	0.15	0.31 4.6	0.34 5.4	3.0	0.13
t							1.11	0.51			3.48	4.61
P value							NS	NS			<0.01	<0.01

Baseline data are expressed as absolute values (l s^{-1}) and percentage of predicted (brackets)

B, before pretreatment; A, after placebo, clemastine or cimetidine

Percentage and absolute fall in MMEF after exercise are calculated from baseline (A)

P values refer to the difference between results after placebo and those after clemastine or cimetidine

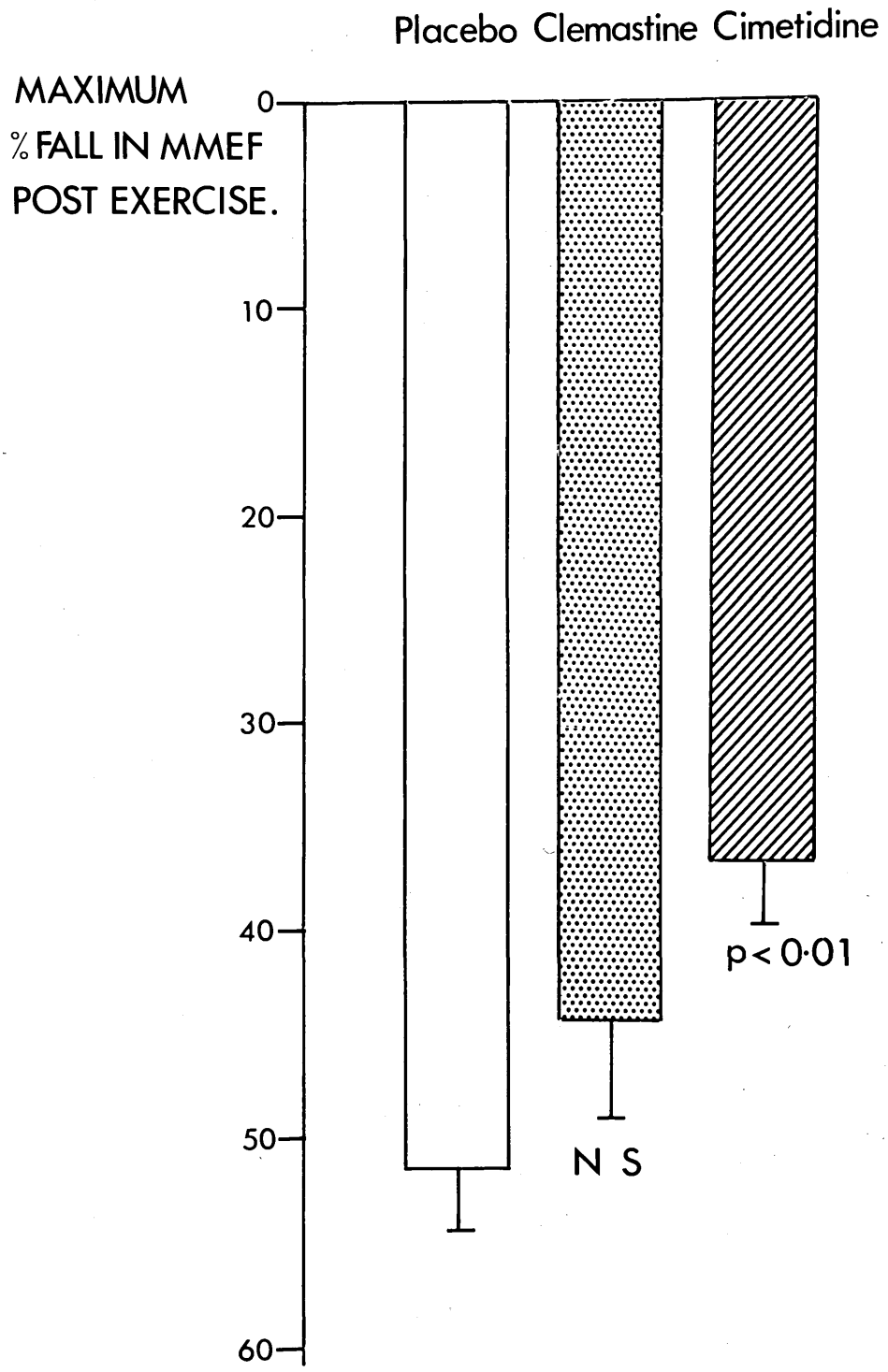

FIGURE 32 EFFECT OF EXERCISE ON MAXIMUM PERCENTAGE FALL IN MMEF AFTER EXERCISE (MEAN $\pm$ SEM) FOLLOWING CLEMASTINE, CIMETIDINE OR SALINE IN ASTHMATIC PATIENTS (N = 10)

APPENDICES

APPENDIX A

DEFINITION OF ASTHMA

There is no generally accepted definition of asthma (Ciba Foundation Study Group No. 38, 1971). Scadding (1977) has suggested asthma be considered as "a disease characterised by wide variations over short periods of time in resistance to flow in intrapulmonary airways", and proposed the following categories:-

(a) Extrinsic atopic asthma due to IgE-mediated hypersensitivity reactions in inhaled antigens commonly present in the air. Often presents with wheezy breathlessness early in life. Extrinsic implies that asthma is precipitated by contact with environmental antigens and atopic refers to the type of hypersensitivity reaction involved. The asthmatic patients investigated in this study would be included in this category.

(b) Extrinsic non-atopic asthma due to reactions between inhaled antigens and antibodies other than IgE.

(c) Intrinsic asthma usually begins later in life, tends to be persistant and have a non-seasonal

incidence. The serum total IgE is not elevated but a blood eosinophilia may be present.

(d) Exercise-induced asthma may be present in both extrinsic and intrinsic types.

(e) Asthma associated with chronic broncho-pulmonary disease.

APPENDIX B

DERIVATION OF PHYSIOLOGICAL MEASUREMENTS

Body Plethysmography

According to Poiseuille's equation:

$$\text{Resistance} = \frac{8\,l\,\eta}{\pi r^4}$$

Where l is the length of tube (airway), r is the radius of the tube, and η is the viscosity of the gas. This equation may not be strictly applicable to the airways, but it can be accepted that large changes in resistance occur with relatively small changes in airway calibre (Pride, 1971). Consequently, the measurement of airways resistance is a very sensitive indirect way of detecting small changes in the size of the airways.

In 1956 a method for measuring airways resistance using a constant volume type of whole-body plethysmograph was introduced (DuBois et al, 1956[a]; DuBois, Botelho & Comroe, 1956[b]). The subject breathes into the box which is closed, and of constant volume. There is an inverse relationship between alveolar and box pressure. The subject pants gently against a closed shutter which occludes flow, and pressures are measured simultaneously in the box and at the mouth. Since no flow is occurring, mouth

pressure will be the same as alveolar pressure. From this procedure a relationship is obtained between alveolar pressure and box pressure: $\Delta P_A / \Delta P_{Box}$ With the shutter open and the subject breathing gently, a relationship between flow and box pressure is obtained $\dot{V} / \Delta P_{Box}$. From these relationships, airways resistance is obtained as follows:

$$\text{Airway resistance} = \frac{\Delta P_A}{\Delta P_{Box}} \times \frac{\Delta P_{Box}}{\dot{V}}$$

In addition, thoracic gas volume can be derived when the subject pants against the closed shutter. The lung volume increases, ΔV, the alveolar pressure falls by an amount ΔP_A and box pressure rises by an amount P_{Box}. From Boyles law, which states that the product of pressure and volume is constant (at constant temperature), the thoracic gas volume is obtained.

$$\text{Thoracic gas volume} = \frac{\Delta V(P_B)}{\Delta P_A}$$

(P_B is barometric pressure)

Flow-volume Curves

Maximal expiratory flow is determined by the static recoil pressure of the lungs and resistance of the upstream segment (i.e. from alveolus to equal pressure point (EPP) (Mead et al, 1967). Since static record pressure of the lungs does not change with helium (He), (Despas et al, 1972), increases in

expiratory flow at 50% vital capacity ($\dot{V}_{50}$) with He are thought to result from a decrease in the resistance of the upstream segment. The resistance of the upstream segment is made up of convective acceleration, frictional resistance to laminar flow and frictional resistance to turbulent flow. Resistance to convective acceleration is dependent upon gas density (P) and is inversely related to the square of the cross-sectional area of EPP.

$$\text{Reynold's number} = \frac{VPD}{2\mu}$$

Where V = linear velocity and equals flow divided by total airway cross-sectional area,

P = gas density

D = airway diameter

μ = gas viscosity

In the peripheral airways, flow is probably laminar, where the total cross-sectional area is large, and linear velocity is low, resulting in a low Reynold's number. Resistance to laminar flow is independent of gas density, but is directly related to gas viscosity (Poiseuille's equation). Turbulent flow occurs in airways with higher Reynold's numbers, resistance then becoming density dependent. Therefore, subjects showing an increase in flow rates on breathing He are thought to have the major site of resistance to

expiratory flow in the large central airways (responders) where in those showing no such increase the major site is thought to be in the small peripheral airways (non-responders).

APPENDIX C

EFFECT OF INHALED PLACEBO IN THE PREVENTION OF EXERCISE-INDUCED ASTHMA

Ten patients with extrinsic asthma were studied (Table XXXVII). FEV_1 was measured in triplicate using a water-sealed spirometer (Godart), the best recording being used for analysis. Exercises were performed on an inclined treadmill and the study was completed within ten days.

After baseline measurements of FEV_1, the following agents were administered by Wright nebuliser during 10 min of tidal breathing: placebo one (saline, 9 g/l, 0.15 mmol/l); placebo two (saline, 9 g/l, 0.15 mmol/l). After 30 min, spirometry was repeated and then at 2, 5, 10, 15 and 20 min after the exercise test. Placebo one and two were given in a random double-blind manner. Statistical analysis was performed using "Student's" paired t test.

Results (Tables XXXVIII, XXXIX, Figure 4)

The baseline values of FEV_1 before and after aerosol administration on the two days were similar ($P > 0.05$). There was no significant difference in the effect of pre-treatment with placebo one or two in preventing the fall in FEV_1 after exercise ($t = 0.44$; $P > 0.30$).

TABLE XXXVII Clinical details of asthmatic patients studied in Chapter II

Patient No	Age (yr)	Sex	Height (cm)	Weight (Kg)	Mean Baseline FEV_1 (l)	% Predicted FEV_1
1 L.H.	18	F	160	47	3.24	108.0
2 W.L.	21	M	166	63	4.47	117.6
3 E.B.	31	F	166	56	3.03	99.3
4 A.S.	25	M	190	80	3.76	81.7
5 W.W.	18	M	174	84	4.17	101.7
6 V.D.	26	F	159	62	2.56	85.3
7 C.W.	19	F	152	54	2.57	90.1
8 R.S.	24	M	175	81	4.90	119.5
9 F.T.	29	F	168	64	3.73	118.4
10 S.S.	25	M	185	70	4.52	100.4

TABLE XXXVIII Maximum fall in FEV_1 after exercise following placebo 1 or 2

Patient No	Placebo 1				Placebo 2			
	Baseline				Baseline			
	B	A	% fall	Absolute fall (l)	B	A	% fall	Absolute fall (l)
1	3.18(106.0)	3.20(106.6)	-26.5	-0.85	3.31(110.3)	3.38(112.6)	-29.6	-1.00
2	4.50(118.0)	4.75(125.0)	-33.6	-1.60	4.45(117.1)	4.65(122.3)	-26.6	-1.24
3	2.98(97.7)	2.97(97.3)	-26.3	-0.78	3.08(100.9)	3.18(104.2)	-44.3	-1.41
4	3.64(79.1)	3.64(79.1)	-20.1	-0.73	3.88(84.3)	3.88(84.3)	-22.7	-0.88
5	4.32(105.3)	4.30(104.8)	-22.1	-0.95	4.02(98.0)	4.05(98.7)	-24.6	-1.02
6	2.71(90.3)	3.09(103.0)	-39.1	-1.21	2.41(80.3)	2.58(86.0)	-39.5	-1.02
7	2.55(89.4)	2.58(90.5)	-35.3	-0.91	2.59(90.8)	2.53(88.7)	-35.9	-0.91
8	4.95(120.0)	4.96(120.9)	-54.0	-2.68	4.85(118.2)	4.93(120.2)	-44.0	-2.17
9	3.75(119.0)	3.73(118.4)	-31.3	-1.17	3.71(117.7)	3.79(120.3)	-28.6	-1.08
10	4.55(101.1)	4.55(101.1)	-26.5	-1.21	4.49(99.7)	4.53(100.6)	-29.5	-1.34
Mean	3.62(102.5)	3.78(104.6)	-31.4	-1.21	3.68(101.7)	3.75(103.7)	-32.5	-1.21
SEM	0.26 4.3	0.26 4.4	3.1	0.18	0.26 4.3	0.26 4.6	2.5	0.12
t							0.44	0.03
P value							>0.30	>0.48

Baseline data are expressed as absolute values (l) and percentage of predicted (brackets)
B, before pretreatment; A, after placebo 1 or placebo 2
Percentage and absolute fall in FEV_1 after exercise are calculated from baseline (A)
P value refers to difference between results after placebo 1 and placebo 2.

TABLE XXXIX Effect of exercise on FEV_1 following placebo 1 and 2 in asthmatic patients (N = 10)

Patient No	Baseline B	Baseline A	Absolute values for FEV_1 after exercise 2min	5min	10min	15min	20min
			PLACEBO 1				
1	3.18	3.20	3.11	2.76	2.35	2.53	2.69
2	4.50	4.75	4.52	3.53	3.15	3.78	3.95
3	2.98	2.97	2.24	2.19	2.25	2.43	2.75
4	3.64	3.64	3.34	3.18	2.91	3.03	3.43
5	4.32	4.30	4.12	3.65	3.35	3.54	3.75
6	2.71	3.09	2.38	1.88	2.04	2.54	2.51
7	2.55	2.58	1.99	2.00	1.75	1.67	1.74
8	4.95	4.96	4.15	3.21	2.28	2.95	3.78
9	3.75	3.73	2.85	2.56	2.75	3.05	3.48
10	4.55	4.55	4.10	3.65	3.34	3.67	3.96
Mean	3.71	3.78	3.28	2.86	2.62	2.92	3.20
SEM	0.27	0.26	0.29	0.21	0.18	0.21	0.23
			PLACEBO 2				
1	3.31	3.38	3.21	2.54	2.38	2.98	3.25
2	4.45	4.65	3.55	3.50	3.48	3.41	3.65
3	3.08	3.18	2.53	1.93	1.77	2.32	2.67
4	3.88	3.88	3.65	3.25	3.00	3.35	3.58
5	4.02	4.05	3.72	3.15	3.03	3.25	3.48
6	2.41	2.58	1.64	1.61	1.56	1.74	1.94
7	2.59	2.53	2.18	1.62	1.67	1.77	1.64
8	4.85	4.93	3.88	2.86	2.76	2.85	3.30
9	3.71	3.79	2.95	2.71	2.79	2.95	3.53
10	4.49	4.53	4.05	3.51	3.19	3.43	3.83
Mean	3.68	3.75	3.14	2.67	2.56	2.80	3.09
SEM	0.26	0.26	0.25	0.23	0.22	0.20	0.24

APPENDIX D

ADDITIONAL TABLES

TABLE XL Effect of inhaled clemastine on Raw and V_{tg} in normal subjects (N = 6)

	Baseline		Time after inhaled clemastine (min)											
			2		5		10		20		30		60	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.16	4.58	0.15	4.59	0.13	4.74	0.13	4.73	0.14	4.78	0.14	4.69	0.17	4.91
R.J.	0.10	3.97	0.12	3.84	0.11	4.03	0.10	4.04	0.12	3.60	0.11	4.25	0.10	4.37
N.T.	0.13	4.27	0.19	3.38	0.17	3.83	0.18	3.46	0.12	4.31	0.10	4.30	0.13	3.85
D.I.	0.22	5.91	0.24	5.64	0.24	5.52	0.27	5.56	0.28	5.64	0.27	5.63	0.29	5.62
K.C.	0.33	4.30	0.22	4.54	0.23	4.45	0.20	4.60	0.25	4.65	0.28	4.70	0.25	4.56
A.L.	0.11	3.45	0.16	3.48	0.15	3.54	0.16	3.54	0.17	3.60	0.18	3.55	0.17	3.50
Mean	0.18	4.41	0.18	4.25	0.17	4.35	0.17	4.32	0.18	4.43	0.18	4.52	0.19	4.47
SEM	0.04	0.34	0.02	0.35	0.02	0.29	0.02	0.33	0.03	0.32	0.03	0.28	0.03	0.31

Raw (kPa $l^{-s}S$); V_{tg} (l)

* Values significantly different from those following saline at that time ($p < 0.05$)

TABLE XLI Effect of inhaled cimetidine on Raw and V_{tg} in normal subjects (N = 6)

	Baseline		Time after inhaled cimetidine (min)											
			2		5		10		20		30		60	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.20	4.81	0.16	4.16	0.19	4.57	0.19	4.46	0.20	4.32	0.19	4.60	0.20	4.62
R.J.	0.13	3.80	0.14	3.92	0.14	3.95	0.14	3.85	0.13	3.95	0.14	4.01	0.12	3.90
N.T.	0.14	4.28	0.15	3.64	0.13	3.83	0.14	4.20	0.14	4.10	0.16	4.15	0.16	4.22
D.I.	0.24	5.37	0.30	5.34	0.29	4.99	0.27	5.09	0.27	5.32	0.25	5.25	0.19	5.41
K.C.	0.31	4.36	0.27	4.41	0.25	4.28	0.22	4.30	0.24	4.35	0.24	4.40	0.25	4.32
A.L.	0.22	3.32	0.19	3.40	0.19	3.42	0.19	3.45	0.20	3.38	0.20	3.35	0.20	3.31
Mean	0.21	4.32	0.20	4.15	0.20	4.17	0.19	4.22	0.20	4.24	0.20	4.29	0.19	4.30
SEM	0.03	0.30	0.03	0.28	0.03	0.23	0.02	0.23	0.02	0.26	0.02	0.26	0.02	0.29

Raw ($kPal^{-s}S$); V_{tg} (l)

* Values significantly different from those following saline at that time ($p < 0.05$)

TABLE XLII Effect of inhaled saline on Raw and V_{tg} in normal subjects (N = 6)

	Baseline		Time after inhaled saline (min)											
			2		5		10		20		30		60	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.22	5.30	0.22	4.56	0.21	4.88	0.23	4.33	0.25	4.52	0.23	4.40	0.22	4.45
R.J.	0.13	3.73	0.12	3.48	0.14	3.25	0.12	3.64	0.11	3.60	0.12	3.55	0.12	3.58
N.T.	0.12	3.92	0.14	3.66	0.13	3.52	0.16	3.60	0.15	4.08	0.14	3.87	0.13	3.89
D.I.	0.36	5.04	0.29	4.87	0.30	5.08	0.30	5.12	0.26	5.01	0.30	5.03	0.32	4.89
K.C.	0.25	4.37	0.31	4.25	0.33	3.85	0.29	3.88	0.28	3.93	0.34	3.96	0.32	3.90
A.L.	0.19	3.25	0.19	3.45	0.20	3.56	0.20	3.42	0.20	3.38	0.20	3.53	0.21	3.47
Mean	0.21	4.27	0.21	4.05	0.22	4.02	0.22	4.00	0.21	4.09	0.22	4.06	0.22	4.03
SEM	0.04	0.32	0.03	0.25	0.03	0.31	0.03	0.26	0.03	0.24	0.04	0.23	0.04	0.22

Raw ($kPal^{-s}S$); V_{tg} (l)

TABLE XLIII Effect of inhaled histamine on Raw and V_{tg} following clemastine in normal subjects (N = 8)

	Baseline				Change in Raw and V_{tg}											
	B		A		Conc.of histamine 1.5		3.1		6.2		12.5		25.0		50.0	
	Raw	V_{tg}	Raw	V_{tg}	(g/l) Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.24	4.95	0.22	4.61	0.20	4.57	0.22	4.68	0.21	4.81	0.21	5.27	0.22	5.58	0.28	5.94
R.J.	0.15	3.01	0.16	3.04	0.13	2.91	0.14	2.75	0.13	2.91	0.13	2.95	0.12	2.84	0.14	2.95
N.T.	0.10	4.29	0.10	4.28	0.10	4.54	0.11	4.44	0.10	4.18	0.12	4.11	0.10	4.25	0.14	4.11
A.L.	0.14	3.78	0.17	3.32	0.15	3.42	0.14	3.35	0.16	3.21	0.14	3.03	0.14	3.24	0.17	3.14
M.K.	0.22	3.18	0.21	2.98	0.24	2.86	0.22	2.97	0.22	2.93	0.19	3.17	0.26	2.96	0.25	3.14
D.I.	0.26	5.06	0.26	5.55	0.25	5.50	0.21	5.45	0.25	5.47	0.24	5.66	0.24	5.09	0.29	5.26
A.McF.	0.24	2.61	0.24	2.41	0.32	2.50	0.36	2.55	0.37	2.27	0.46	2.53	0.49	2.78	0.69	3.07
K.C.	0.19	4.15	0.16	4.19	0.18	4.12	0.19	4.13	0.22	4.18	0.21	4.42	0.22	4.33	0.21	4.68
Mean	0.19	3.09	0.19	3.80	0.20	3.80	0.20	3.79	0.21	3.75	0.21**	3.89	0.22**	3.88	0.27*	4.04*
SEM	0.02	0.93	0.02	0.37	0.03	0.37	0.03	0.37	0.03	0.39	0.04	0.41	0.04	0.38	0.06	0.41

B, before pre-treatment; A, after clemastine

Raw ($kPa1^{-S}S$); V_{tg} (1)

Values significantly different from those with saline pre-treatment at that concentration * $p < 0.05$

** $p < 0.01$

TABLE XLIV Effect of inhaled histamine on Raw and V_{tg} following cimetidine in normal subjects (N = 8)

	Baseline				Change in Raw and V_{tg}											
	B		A		Conc.of histamine 1.5		3.1		6.2		12.5		25.0		50.0	
	Raw	V_{tg}	Raw	V_{tg}	(g/l) Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.20	5.10	0.22	5.11	0.22	5.22	0.23	5.39	0.26	5.34	0.28	5.75	0.32	5.91	0.31	6.19
R.J.	0.20	3.38	0.19	3.34	0.18	3.34	0.17	3.18	0.20	3.23	0.24	3.14	0.35	3.41	0.56	3.72
N.T.	0.13	4.38	0.15	3.97	0.15	3.65	0.14	4.02	0.15	3.84	0.21	3.93	0.22	3.98	0.37	4.23
A.L.	0.14	3.17	0.17	2.84	0.18	2.94	0.17	3.14	0.20	3.04	0.18	2.80	0.20	2.93	0.32	2.87
M.K.	0.25	3.61	0.34	3.24	0.33	3.21	0.35	3.28	0.33	3.28	0.39	3.08	0.51	3.10	0.84	3.36
D.I.	0.24	5.65	0.22	5.65	0.24	5.54	0.24	5.56	0.22	5.39	0.22	5.39	0.29	5.55	0.83	6.18
A.McF	0.28	2.20	0.24	2.41	0.31	2.40	0.34	2.43	0.38	2.63	0.56	2.91	0.65	3.42	0.90	3.47
K.C.	0.21	3.98	0.19	4.03	0.23	4.05	0.26	4.09	0.29	4.21	0.31	4.22	0.33	4.40	0.35	4.53
Mean	0.21	3.93	0.22	3.82	0.23	3.79	0.24	3.89	0.25	3.87	0.30	3.90	0.36	4.09	0.56	4.32
SEM	0.02	0.39	0.03	0.39	0.02	0.39	0.03	0.39	0.03	0.37	0.04	0.41	0.05	0.40	0.09	0.45

B, before pre-treatment; A, after cimetidine

Raw ($kPal^{-s}S$); V_{tg} (l)

* Values significantly different from saline pre-treatment at that concentration ($p < 0.05$)

TABLE XLV Effect on inhaled histamine on Raw and V_{tg} following saline in normal subjects (N = 8)

	Baseline				Change in Raw and V_{tg}											
	B		A		Conc.of histamine 1.5		3.1		6.2		12.5		25.0		50.0	
	Raw	V_{tg}	Raw	V_{tg}	(g/l) Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.17	4.51	0.17	4.48	0.17	5.13	0.18	5.10	0.19	5.20	0.22	5.48	0.26	5.81	0.27	6.18
R.J.	0.19	3.37	0.19	3.27	0.20	3.26	0.18	3.35	0.22	3.15	0.24	3.30	0.35	3.30	0.41	3.99
N.T.	0.16	3.84	0.17	3.98	0.15	4.37	0.16	4.15	0.14	4.27	0.18	4.40	0.24	3.96	0.35	4.35
A.L.	0.14	2.96	0.21	2.69	0.18	3.23	0.19	2.82	0.17	3.09	0.21	3.06	0.20	2.82	0.25	3.16
M.K.	0.33	3.16	0.38	2.94	0.30	2.92	0.32	2.84	0.31	2.96	0.33	2.91	0.56	3.18	1.04	3.91
D.I.	0.26	5.48	0.24	5.56	0.21	5.62	0.21	5.52	0.21	5.52	0.26	5.69	0.35	5.96	0.49	6.40
A.McF.	0.24	2.46	0.24	2.54	0.26	2.39	0.29	2.52	0.45	2.71	0.66	3.12	0.78	3.50	0.82	3.56
K.C.	0.19	4.00	0.17	4.03	0.20	4.20	0.22	4.23	0.24	4.40	0.28	4.42	0.30	4.50	0.32	4.50
Mean	0.21	3.72	0.22	3.69	0.21	3.89	0.22	3.82	0.24	3.91	0.30	4.05	0.38	4.13	0.49	4.51
SEM	0.02	0.34	0.02	0.36	0.02	0.40	0.02	0.39	0.03	0.38	0.05	0.39	0.07	0.42	0.10	0.42

B, before pre-treatment; A, after saline

Raw ($kPa l^{-1} s$); V_{tg} (l)

TABLE XLVI Effect of inhaled methacholine on Raw and V_{tg} following inhaled ipratropium in normal subjects (N = 8)

	Baseline				Change in Raw and V_{tg}									
	B		A		Conc.of methacholine (g/l) 3.1		6.2		12.5		25.0		50.0	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.25	4.72	0.19	4.63	0.19	4.55	0.18	4.57	0.17	4.62	0.17	4.65	0.17	4.70
R.J.	0.16	2.71	0.13	2.80	0.10	2.85	0.11	2.75	0.12	2.79	0.10	2.82	0.11	2.83
N.T.	0.09	4.13	0.08	4.18	0.08	3.83	0.08	3.62	0.09	3.49	0.13	3.88	0.10	3.80
A.L.	0.19	3.27	0.16	3.17	0.15	3.09	0.15	3.24	0.17	3.15	0.17	3.12	0.19	3.02
M.K.	0.32	3.02	0.24	3.03	0.11	3.03	0.23	3.09	0.13	3.03	0.27	3.10	0.24	3.07
D.I.	0.25	5.43	0.19	5.39	0.24	5.29	0.22	5.30	0.18	5.35	0.22	5.34	0.24	5.43
A.McF.	0.24	2.32	0.20	2.35	0.19	2.30	0.20	2.28	0.20	2.31	0.19	2.15	0.19	2.10
K.C.	0.18	3.99	0.14	3.99	0.15	3.97	0.15	3.98	0.16	3.95	0.14	3.99	0.15	4.03
Mean	0.21	3.70	0.17	3.69	0.15	3.61	0.17*	3.60**	0.15*	3.59**	0.17*	3.63**	0.17**	3.62**
SEM	0.02	0.37	0.02	0.36	0.02	0.35	0.02	0.35	0.01	0.36	0.02	0.37	0.02	0.38

B, before pre-treatment; A, after ipratropium

Raw ($kPal^{-s}S$); V_{tg} (l)

Values significantly different from saline pre-treatment at that concentration * $p < 0.05$

TABLE XLVII Effect of inhaled methacholine on Raw and V_{tg} following clemastine in normal subjects (N = 8)

	Baseline				Change in Raw and V_{tg}									
	B		A		Conc.of methacholine	3.1		6.2		12.5		25.0		50.0	
	Raw	V_{tg}	Raw	V_{tg}	(g/l)	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.19	4.69	0.16	4.84		0.19	4.80	0.19	4.85	0.19	4.92	0.21	5.16	0.26	5.23
R.J.	0.13	2.79	0.13	2.88		0.15	2.91	0.18	2.99	0.32	3.05	0.61	3.36	0.58	3.62
N.T.	0.13	3.95	0.12	3.43		0.14	3.73	0.12	3.44	0.15	3.90	0.16	3.64	0.20	3.89
A.L.	0.14	3.79	0.15	3.60		0.14	3.90	0.13	3.95	0.15	3.82	0.16	4.23	0.27	4.30
M.K.	0.32	2.95	0.33	2.93		0.28	3.23	0.32	3.15	0.41	3.16	0.70	3.25	0.77	3.80
D.I.	0.24	5.53	0.22	5.68		0.24	5.64	0.26	5.51	0.26	5.72	0.98	6.01	1.40	6.51
A.McF.	0.27	2.45	0.23	2.46		0.22	2.56	0.25	2.54	0.24	2.73	0.28	2.98	0.31	3.71
K.C.	0.18	4.20	0.21	4.15		0.23	4.33	0.23	4.34	0.29	4.42	0.50	4.61	0.53	4.68
Mean	0.15	3.79	0.14	3.75		0.20	3.89	0.21	3.85	0.25	3.97	0.45	4.16	0.54	4.47
SEM	0.02	0.37	0.01	0.38		0.02	0.36	0.02	0.36	0.03	0.36	0.11	0.37	0.14	0.35

B, before pre-treatment; A, after clemastine

Raw ($kPal^{-S}S$); V_{tg} (l)

* Values significantly different from saline pretreatment at that concentration ($p < 0.05$)

TABLE XLVIII Effect of inhaled methacholine on Raw and V_{tg} following saline in normal subjects (N = 8)

	Baseline				Change in Raw and V_{tg}									
	B		A		Conc.of methacholine	3.1		6.2		12.5		25.0		50.0	
	Raw	V_{tg}	Raw	V_{tg}	(g/l)	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
I.W.	0.22	5.12	0.20	4.75		0.18	5.13	0.20	5.47	0.22	5.67	0.27	5.91	0.28	6.10
R.J.	0.12	2.88	0.13	2.94		0.15	2.88	0.22	2.98	0.33	3.20	0.48	3.73	0.61	3.87
N.T.	0.11	4.65	0.10	4.69		0.11	4.48	0.10	4.37	0.11	4.30	0.13	4.33	0.21	4.10
A.L.	0.15	3.77	0.15	3.80		0.14	3.90	0.14	4.21	0.15	4.20	0.17	4.32	0.21	4.40
M.K.	0.30	2.90	0.26	2.95		0.23	3.02	0.26	3.15	0.29	3.12	0.40	3.20	0.81	3.75
D.I.	0.22	5.60	0.21	5.54		0.21	5.60	0.18	5.58	0.24	5.63	0.58	5.98	0.93	6.30
A.McF.	0.26	2.39	0.26	2.46		0.27	2.39	0.26	2.55	0.27	2.83	0.36	2.99	0.35	3.35
K.C.	0.19	4.10	0.18	4.07		0.16	4.15	0.19	4.21	0.24	4.43	0.30	4.49	0.38	4.62
Mean	0.20	3.93	0.19	3.90		0.18	3.94	0.19	4.07	0.23	4.17	0.34	4.37	0.47	4.56
SEM	0.02	0.41	0.02	0.38		0.02	0.40	0.02	0.39	0.03	0.39	0.05	0.39	0.10	0.38

B, before pre-treatment; A, after saline

Raw ($kPal^{-s}S$); V_{tg} (l)

TABLE XLIX Effect of infused dopamine on radial pulse rate in normal subjects (N = 6)

	Pre-infusion baseline	Time after dopamine infusion (min)					
		1	3	5	10	15	20
D.A.	75	75	74	75	75	76	77
M.D.	78	77	75	73	77	77	77
D.I.	85	87	88	88	89	87	87
K.S.	88	82	82	83	83	84	84
T.H.	82	81	80	81	80	82	81
K.P.	79	77	78	76	80	82	81
Mean	81	80	79	79	80	81	81
SEM	1.9	1.8	2.1	2.3	2.0	1.7	1.6
t		1.23	1.38	1.43	0.40	0.16	0.00
P value		NS	NS	NS	NS	NS	NS

Pulse rate (beats/min)

TABLE L Effect of infused dopamine on radial pulse rate in asthmatic patients (N = 8)

Study No	Pre-infusion baseline	Infusion baseline	Time after dopamine infusion (min)			
			0	4	9	19
1	96	96	96	96	96	96
2	84	78	76	72	80	76
3	64	62	64	58	60	62
4	88	88	88	88	84	84
5	86	80	80	80	80	81
6	72	80	80	78	78	74
7	80	78	80	74	72	72
8	95	92	92	84	88	93
Mean	83	82	82	79	80	80
SEM	3.9	3.7	3.5	4.0	3.8	4.1
t			0.55	0.28	2.16	1.98
P value			NS	NS	NS	NS

Infusion baseline refers to values after dextrose (50 g/l) infusion without dopamine

Pulse rate (beats/min)

TABLE LI Effect of infused dopamine on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in normal subjects (N = 6)

	Pre-infusion baseline		Time after dopamine infusion (min)									
			0		4		11		14		19	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
D.A.	110	75	115	75	115	75	115	75	115	70	110	70
M.D.	115	80	110	78	115	78	115	78	115	80	115	85
D.I.	120	60	115	65	120	65	125	65	120	60	120	65
K.S.	130	85	130	80	130	80	125	75	130	75	130	80
T.H.	120	70	125	70	125	75	120	70	120	70	120	75
K.P.	115	80	115	80	110	80	115	80	115	80	115	75
Mean	118	75	118	75	119	75	119	74	119	73	118	75
SEM	2.7	3.6	3.1	2.4	3.0	2.3	2.0	2.2	2.4	3.1	2.8	2.9
t			0.00	0.25	0.54	0.31	0.54	0.58	1.00	1.46	0.00	0.38
P value			NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Blood pressure (mmHg)

TABLE LII Effect of infused dopamine on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in asthmatic patients (N = 8)

Study No	Pre-infusion baseline		Infusion baseline		Time after dopamine infusion (min)							
					0		4		9		19	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1	130	90	135	90	140	85	130	80	130	80	125	75
2	120	82	118	78	130	80	135	85	125	80	120	80
3	115	80	118	78	115	75	115	75	115	75	115	75
4	110	80	105	70	105	60	110	65	110	65	110	70
5	135	90	135	85	135	85	135	85	135	85	135	85
6	130	80	130	80	150	85	140	85	135	85	125	80
7	120	60	125	65	115	60	120	70	105	70	115	70
8	120	70	115	70	125	70	120	70	120	70	120	70
Mean	123	79	123	77	127	75	126	77	122	76	121	76
SEM	3.0	3.5	3.7	2.9	5.2	3.8	3.8	2.8	4.0	2.6	2.7	2.0
t					1.26	1.19	1.08	0.06	0.23	0.41	0.93	0.65
P value					NS	NS	NS	NS	NS	NS	NS	NS

Infusion baseline refers to values after dextrose (50 g/l) infusion without dopamine

Blood pressure (mmHg)

TABLE LIII Effect of infused dopamine on Raw and V_{tg} in normal subjects (N = 6) and asthmatic patients (N = 8)

Group	Pre-infusion baseline		Infusion baseline		Time after dopamine infusion (min)											
					1		3		5		10		15		20	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
Normals																
D.A.	0.17	4.06			0.17	4.16	0.14	3.87	0.13	4.38	0.17	4.69	0.20	4.04	0.16	4.17
M.D.	0.18	4.77			0.16	4.56	0.18	4.88	0.18	4.77	0.15	4.77	0.15	4.71	0.15	4.87
D.I.	0.24	4.29			0.21	4.21	0.20	4.83	0.19	5.42	0.25	4.41	0.23	4.59	0.21	4.60
K.S.	0.17	4.86			0.20	3.21	0.16	4.22	0.19	4.02	0.19	4.08	0.15	4.06	0.18	4.21
T.H.	0.17	4.02			0.19	3.55	0.21	4.38	0.22	3.97	0.23	4.23	0.16	4.46	0.20	4.53
K.P.	0.17	2.25			0.14	2.80	0.12	3.24	0.10	3.57	0.18	2.36	0.16	2.77	0.14	2.92
Mean	0.18	4.04			0.18	3.75	0.17	4.24	0.17	4.86	0.20	4.09	0.18	4.11	0.17	4.22
SEM	0.01	0.39			0.01	0.28	0.01	0.25	0.02	0.50	0.02	0.36	0.01	0.29	0.01	0.28
Asthmatics																
Study No																
1	0.37	2.86	0.41	2.99	0.49	3.02			0.44	3.22	0.45	3.03			0.47	2.75
2	0.55	3.33	0.61	3.91	0.50	4.26			0.62	3.78	0.52	3.70			0.46	3.64
3	0.53	2.90	0.60	3.01	0.56	2.90			0.62	2.87	0.50	3.17			0.61	2.96
4	0.55	2.56	0.54	2.53	0.68	2.26			0.53	2.72	0.62	2.47			0.62	2.42
5	0.28	5.48	0.28	5.34	0.24	5.92			0.22	6.01	0.23	6.17			0.26	5.49
6	0.34	7.17	0.37	7.41	0.46	6.60			0.33	7.91	0.49	7.22			0.47	7.06
7	0.24	4.47	0.37	4.20	0.38	4.51			0.49	4.79	0.52	4.96			0.57	5.32
8	0.42	2.99	0.44	2.11	0.45	2.63			0.50	2.69	0.49	2.40			0.42	3.00
Mean	0.41	3.97	0.45	3.94	0.47	4.01			0.47	4.25	0.48	4.14			0.48	4.08
SEM	0.04	0.57	0.04	0.61	0.04	0.56			0.05	0.66	0.04	0.63			0.04	0.59

Infusion baseline refers to values after dextrose (50 g/l) infusion without dopamine

Raw ($kPal^{-S}S$) V_{tg} (l)

* Values significantly different from baseline values ($p < 0.05$)

TABLE LIV Effect of infused thymoxamine alone and in combination with dopamine on Raw and V_{tg} in Asthmatic patients (N = 6)

Study No	Baseline		Thymoxamine alone		Change after thymoxamine plus dopamine			
					1 min		5 min	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
3	0.61	2.96	0.56	3.00	0.48	3.26	0.45	3.31
4	0.62	2.42	0.59	2.59	0.52	2.60	0.67	2.67
5	0.26	5.49	0.22	6.06	0.23	6.06	0.24	5.67
6	0.26	7.06	0.34	7.90	0.30	8.26	0.34	8.08
7	0.55	5.49	0.55	5.82	0.47	5.03	0.37	5.16
8	0.54	2.92	0.44	3.10	0.51	3.17	0.52	2.97
Mean	0.47	4.39	0.45	4.74	0.42	4.73	0.43	4.64
SEM	0.07	0.77	0.06	0.88	0.05	0.88	0.06	0.85

Raw ($kPal^{-s}$); V_{tg}(l)

* Values significantly different from values following thymoxamine alone ($p < 0.05$)

TABLE LV Effect of inhaled dopamine on Raw and V_{tg} in normal subjects (N = 6) and asthmatic patients (N = 6)

Group	Baseline		Post saline		Dose of dopamine (g/l)					
					0.5		1.0		2.0	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
Normals										
K.P.	0.10	2.84	0.11	2.52	0.12	2.24	0.13	2.27	0.12	2.25
D.A.	0.10	4.24	0.10	3.99	0.13	3.95	0.12	3.96	0.12	3.84
A.C.	0.16	3.04	0.17	3.27	0.16	3.47	0.15	3.76	0.15	3.69
D.I.	0.21	4.13	0.24	3.88	0.19	4.66	0.20	4.14	0.18	4.58
B.R.	0.21	3.00	0.22	2.98	0.21	3.20	0.20	3.12	0.20	3.20
B.McD.	0.10	3.00	0.10	3.10	0.10	3.20	0.10	3.30	0.11	3.15
Mean	0.15	3.37	0.16	3.29	0.15	3.45	0.15	3.42	0.15	3.45
SEM	0.02	0.26	0.02	0.23	0.02	0.33	0.02	0.28	0.01	0.32
Asthmatics										
Study No										
2	0.35	3.66	0.34	4.65	0.41	4.13	0.33	4.46	0.43	4.04
7	0.45	4.43	0.46	4.30	0.41	4.36	0.43	4.56	0.40	4.42
9	0.20	4.21	0.22	4.32	0.24	4.30	0.22	4.29	0.24	4.19
10	0.64	3.54	0.69	4.24	0.65	4.50	0.57	4.58	0.71	3.92
11	0.56	4.43	0.63	4.92	0.72	4.96	0.68	5.08	0.68	5.08
12	0.18	3.52	0.19	3.65	0.22	3.65	0.15	3.46	0.22	3.65
Mean	0.39	3.96	0.42	4.35	0.44	4.32	0.39	4.40	0.45	4.22
SEM	0.08	0.18	0.08	0.17	0.08	0.17	0.08	0.22	0.08	0.20

Raw ($kPal^{-s}S$) V_{tg} (l)

* Values significantly different from post saline baseline ($P < 0.05$)

TABLE LVI Effect of inhaled bupivacaine or saline on Raw and V_{tg} in normal subjects (N = 5)

Subject	Baseline		Change in Raw and V_{tg} after inhalation									
			1 min		5 min		10 min		15 min		20 min	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
						SALINE						
I.W.	0.15	4.56	0.14	4.54	0.13	4.72	0.14	4.65	0.14	4.62	0.15	4.48
R.G.	0.13	3.73	0.13	3.78	0.13	3.70	0.14	3.69	0.14	3.65	0.14	3.71
D.I.	0.26	4.30	0.26	4.35	0.27	4.28	0.27	4.15	0.27	4.10	0.25	4.15
K.C.	0.26	3.95	0.27	3.86	0.26	3.96	0.26	3.99	0.27	3.89	0.26	3.96
K.P.	0.07	3.15	0.08	2.95	0.09	2.99	0.08	3.21	0.08	3.25	0.08	3.21
Mean	0.17	3.94	0.18	3.90	0.18	3.93	0.18	3.94	0.18	3.90	0.18	3.90
SEM	0.03	0.24	0.03	0.27	0.03	0.29	0.03	0.23	0.03	0.22	0.03	0.21
						BUPIVACAINE						
I.W.	0.16	4.30	0.14	4.53	0.14	4.56	0.15	4.60	0.16	4.35	0.16	4.36
R.G.	0.11	3.90	0.10	3.95	0.11	3.72	0.11	3.78	0.11	3.82	0.11	3.81
D.I.	0.28	4.15	0.27	4.10	0.29	4.13	0.29	4.13	0.29	4.15	0.29	4.13
K.C.	0.26	3.93	0.26	3.98	0.25	4.11	0.26	4.09	0.26	4.03	0.25	4.13
K.P.	0.07	3.18	0.09	3.17	0.09	3.19	0.08	3.35	0.08	3.25	0.08	3.28
Mean	0.18	3.89	0.17	3.95	0.18	3.94	0.18	3.99	0.18	3.92	0.18	3.94
SEM	0.04	0.19	0.03	0.22	0.04	0.23	0.04	0.20	0.04	0.18	0.03	0.18

Raw ($kPal^{-s}S$); V_{tg} (l)

* Values significantly different from saline pre-treatment at that time ($p < 0.05$)

TABLE LVII Effect of inhaled bupivacaine on Raw and V_{tg} in asthmatic patients (N = 5)

Patient No	Pre-treatment	Baseline B Raw	Baseline B V_{tg}	Baseline A Raw	Baseline A V_{tg}	Change in Raw and V_{tg} after bupivacaine: 1 min Raw	1 min V_{tg}	5 min Raw	5 min V_{tg}	10 min Raw	10 min V_{tg}	15 min Raw	15 min V_{tg}	20 min Raw	20 min V_{tg}
1	Saline	0.45	3.00	0.39	3.18	1.21	4.07	1.17	4.25	0.95	4.39	0.91	4.35	0.80	4.29
2		0.35	6.20	0.36	5.96	0.78	6.69	0.82	6.32	0.93	6.51	0.97	6.51	0.96	6.52
3		0.19	4.80	0.19	4.80	0.28	4.75	0.28	4.57	0.31	4.18	0.30	4.31	0.28	4.43
4		0.13	3.63	0.12	3.90	0.14	3.98	0.19	3.96	0.22	3.66	0.21	3.50	0.18	3.53
5		0.39	3.22	0.39	3.14	0.92	3.81	1.00	4.00	0.89	4.39	0.84	4.31	0.99	4.34
Mean		0.30	4.17	0.29	4.20	0.67	4.66	0.69	4.62	0.66	4.63	0.65	4.60	0.64	4.62
SEM		0.06	0.59	0.05	0.53	0.20	0.53	0.19	0.43	0.16	0.49	0.16	0.50	0.17	0.50
1	Ipratropium	0.36	3.83	0.27	3.19	0.28	3.45	0.35	3.23	0.33	3.37	0.37	3.13	0.35	3.21
2		0.30	6.01	0.19	5.33	0.19	5.48	0.21	5.30	0.20	5.65	0.19	5.40	0.19	5.51
3		0.25	4.62	0.23	4.22	0.26	4.21	0.27	4.57	0.30	4.44	0.40	4.48	0.35	4.42
4		0.17	3.80	0.09	3.81	0.09	3.31	0.08	3.62	0.09	3.64	0.09	3.63	0.09	3.51
5		0.53	3.35	0.36	3.02	0.37	3.15	0.39	3.35	0.40	3.39	0.40	3.41	0.39	3.37
Mean		0.32	4.32	0.23	3.91	0.24*	3.92*	0.27*	4.01	0.27*	4.10	0.29	4.01	0.27	4.00
SEM		0.06	0.46	0.04	0.41	0.04	0.43	0.05	0.39	0.05	0.43	0.06	0.41	0.05	0.43

B, before pre-treatment; A, after saline or ipratropium

Raw ($kPal^{-s}S$); V_{tg} (l)

* Values significantly different from saline pre-treatment at that time ($p < 0.05$)

TABLE LVIII Effect of inhaled methacholine on Raw and V_{tg} in normal subjects (N = 5)

Subject	Pre-treatment	Baseline B Raw	Baseline B V_{tg}	Baseline A Raw	Baseline A V_{tg}	Change in Raw and V_{tg} after methacholine (10 g/l) 1 min Raw	1 min V_{tg}	5 min Raw	5 min V_{tg}	10 min Raw	10 min V_{tg}
I.W.	Saline	0.16	4.97	0.17	4.70	0.24	5.30	0.20	5.66	0.24	5.77
K.C.		0.16	5.23	0.15	4.85	0.28	6.01	0.27	6.50	0.32	6.06
R.G.		0.14	3.79	0.13	3.91	0.37	3.52	0.37	3.50	0.33	3.44
R.S.		0.14	4.36	0.17	3.51	0.42	4.48	0.31	4.84	0.32	4.50
D.I.		0.25	5.58	0.26	5.68	1.06	6.26	0.64	5.84	0.58	6.51
Mean		0.17	4.79	0.18	4.53	0.47	5.11	0.36	5.27	0.36	5.26
SEM		0.02	0.32	0.02	0.38	0.15	0.50	0.07	0.52	0.05	0.56
I.W.	Ipratropium	0.15	4.93	0.15	4.70	0.12	4.88	0.14	4.80	0.13	4.66
K.C.		0.15	4.99	0.12	4.91	0.12	4.90	0.12	4.83	0.12	4.85
R.G.		0.11	3.45	0.08	3.57	0.06	3.84	0.04	3.28	0.05	3.70
R.S.		0.17	3.91	0.12	3.87	0.11	3.95	0.11	3.96	0.11	3.91
D.I.		0.26	5.53	0.21	5.43	0.21	5.26	0.24	5.19	0.21	5.34
Mean		0.17	4.56	0.14	4.50	0.12*	4.57	0.13*	4.41	0.12*	4.49
SEM		0.02	0.38	0.02	0.34	0.02	0.28	0.03	0.35	0.02	0.30
I.W.	Bupivacaine	0.18	5.33	0.16	5.14	0.24	5.64	0.26	5.52	0.27	5.59
K.C.		0.15	4.94	0.17	5.17	0.22	5.56	0.25	5.70	0.22	6.01
R.G.		0.09	4.38	0.12	3.48	0.28	3.83	0.20	3.86	0.22	3.31
R.S.		0.15	4.15	0.19	3.83	0.38	3.99	0.29	4.20	0.27	4.04
D.I.		0.27	4.89	0.28	5.36	0.38	5.58	0.45	5.69	0.44	5.94
Mean		0.17	4.74	0.18	4.60	0.30	4.92	0.29	4.99	0.28	4.98
SEM		0.03	0.21	0.03	0.39	0.03	0.41	0.04	0.04	0.04	0.55

B, before pre-treatment; A, after saline, ipratropium or bupivacaine

Raw ($kPal^{-S}S$); V_{tg} (l)

* Values significantly different from saline pre-treatment at that time ($p < 0.05$)

TABLE LIX Effect of inhaled methacholine on Raw and V_{tg} in asthmatic patients (N = 6)

Patient No	Pre-treatment	Baseline B Raw	Baseline B V_{tg}	Baseline A Raw	Baseline A V_{tg}	Change in Raw and V_{tg} after methacholine (1 g/l) 1 min Raw	1 min V_{tg}	5 min Raw	5 min V_{tg}	10 min Raw	10 min V_{tg}
1	Saline	0.15	2.70	0.56	2.71	1.83	3.57	1.49	3.95	1.37	3.89
2		0.29	4.93	0.27	4.85	2.04	4.89	1.79	5.60	1.69	5.91
3		0.68	3.40	0.71	3.41	1.20	3.61	0.49	3.82	0.39	3.81
4		0.19	3.60	0.18	3.66	0.64	3.72	0.57	3.93	0.44	3.94
5		0.20	5.60	0.24	5.53	0.89	5.60	0.71	5.61	0.21	5.63
6		0.22	3.23	0.22	3.32	0.51	3.72	0.37	3.89	0.30	3.93
Mean		0.35	3.91	0.34	3.91	1.18	4.18	0.90	4.47	0.73	4.52
SEM		0.08	0.45	0.06	0.43	0.26	0.35	0.24	0.36	0.26	0.40
1	Ipratropium	0.68	2.93	0.45	2.82	0.46	2.91	0.50	2.75	0.51	2.58
2		0.38	4.63	0.27	4.64	0.26	4.59	0.27	4.63	0.25	4.69
3		0.69	3.51	0.29	3.47	0.29	3.52	0.29	3.51	0.27	3.47
4		0.17	3.45	0.13	3.23	0.14	3.03	0.14	3.25	0.13	3.31
5		0.33	5.40	0.19	5.48	0.18	5.48	0.19	5.47	0.19	5.42
6		0.23	3.51	0.17	3.37	0.17	3.37	0.16	3.42	0.16	3.39
Mean		0.39	3.91	0.25	3.84	0.25*	3.82*	0.26*	3.84*	0.25*	3.81*
SEM		0.07	0.37	0.04	0.41	0.05	0.41	0.05	0.41	0.05	0.42

B, before pre-treatment; A, after saline or ipratropium

Raw ($kPal^{-s}S$); V_{tg} (l)

* Values significantly different from saline pretreatment at that time ($p < 0.05$)

TABLE LX Effect of inhaled histamine (2 g/l) on sGaw in normal subjects (N = 6)

Subjects	Baseline sGaw ($s^{-1}kPa^{-1}$)		Change in sGaw after histamine (2 g/l)		
	B	A	1 min	5 min	10 min
D.I.	0.93	0.88	-0.07	-0.06	-0.10
I.W.	1.08	1.07	-0.24	-0.08	-0.05
K.C.+	1.56	1.45	-0.13	-0.23	-0.19
A.G.	2.60	2.75	-0.43	-0.41	-0.32
R.G.+	2.02	2.16	-1.05	-1.01	-0.73
N.T.+	1.25	1.37	-0.17	-0.29	-0.07
Mean	1.57	1.61	-0.35	-0.35	-0.24
SEM	0.25	0.28	0.14	0.14	0.10

+ Subjects with upper respiratory tract infection

B, before pre-treatment; A, after saline

TABLE LXI Effect of inhaled histamine (2 g/l) on Raw and V_{tg} in normal subjects (N = 6)

Subjects	Baseline				Change in Raw and V_{tg} after histamine (2 g/l)					
	B		A		1 min		5 min		10 min	
	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}	Raw	V_{tg}
D.I.	0.18	5.89	0.20	5.70	0.21	5.82	0.22	5.50	0.22	5.85
I.W.	0.17	5.36	0.18	5.01	0.23	5.19	0.19	5.31	0.19	5.09
K.C.+	0.16	3.91	0.17	3.87	0.19	3.93	0.20	3.97	0.19	4.06
A.G.	0.10	3.56	0.10	3.57	0.11	3.69	0.11	3.73	0.11	3.71
R.G.+	0.11	4.43	0.13	3.69	0.24	3.67	0.25	3.49	0.19	3.61
N.T.+	0.17	4.71	0.15	4.94	0.16	5.10	0.21	4.27	0.18	4.17
Mean	0.15	4.64	0.15	4.46	0.19	4.57	0.20	4.38	0.18	4.42
SEM	0.01	0.35	0.01	0.35	0.02	0.37	0.01	0.34	0.01	0.35

+ Subjects with upper respiratory tract infection

B, before pre-treatment; A, after saline

Raw ($kPal^{-s}S$); V_{tg} (l)

TABLE LXII Effect of inhaled histamine (5 g/l) on Raw and V_{tg} in normal subjects (N = 6)

Subjects	Pre-treatment	Baseline B Raw	Baseline B V_{tg}	Baseline A Raw	Baseline A V_{tg}	Change in Raw and V_{tg} after histamine (5 g/l) 1 min Raw	1 min V_{tg}	5 min Raw	5 min V_{tg}	10 min Raw	10 min V_{tg}
D.I.	Saline	0.25	5.98	0.27	5.40	0.34	5.56	0.38	5.47	0.32	5.48
I.W.		0.13	5.56	0.18	4.64	0.22	5.66	0.26	5.45	0.24	5.06
A.G.+		0.14	2.96	0.17	2.87	0.36	3.25	0.23	3.71	0.21	3.22
K.C.+		0.16	4.04	0.17	3.68	0.29	3.51	0.24	4.01	0.24	3.80
R.G.+		0.08	4.18	0.08	4.19	0.20	4.04	0.24	3.70	0.16	3.84
N.T.+		0.17	4.43	0.13	4.89	0.20	4.44	0.25	4.41	0.23	4.21
Mean		0.16	4.52	0.17	4.28	0.27	4.41	0.27	4.46	0.23	4.27
SEM		0.02	0.44	0.02	0.37	0.02	0.42	0.02	0.33	0.02	0.35
D.I.	Ipratropium	0.21	6.02	0.16	5.56	0.21	5.62	0.29	6.04	0.26	6.16
I.W.		0.20	5.31	0.15	5.33	0.15	5.55	0.19	5.13	0.20	5.04
A.G.+		0.15	3.04	0.10	3.10	0.12	3.39	0.14	3.08	0.15	3.11
K.C.+		0.18	3.88	0.16	4.08	0.16	3.96	0.20	3.79	0.24	4.13
R.G.+		0.09	4.14	0.07	3.72	0.06	4.17	0.08	3.90	0.09	4.13
N.T.+		0.13	4.26	0.12	4.06	0.12	4.26	0.12	4.21	0.12	3.88
Mean		0.16	4.44	0.13	4.31	0.14*	4.49	0.17*	4.36	0.18	4.41
SEM		0.01	0.43	0.01	0.39	0.02	0.37	0.03	0.43	0.02	0.43
D.I.	Bupivacaine	0.21	5.63	0.20	5.35	0.26	5.63	0.33	5.77	0.29	5.52
I.W.		0.15	4.49	0.13	4.88	0.27	5.46	0.27	4.66	0.20	4.86
A.G.+		0.09	3.32	0.11	3.10	0.32	3.57	0.28	3.57	0.22	3.58
K.C.+		0.19	4.15	0.29	3.63	0.42	4.75	0.46	4.53	0.27	4.29
R.G.+		0.11	3.29	0.14	3.35	0.31	3.83	0.32	3.94	0.24	3.78
N.T.+		0.16	3.59	0.14	3.46	0.22	3.92	0.20	3.69	0.19	3.78
Mean		0.15	4.08	0.17	3.96	0.30	4.53	0.31	4.36	0.24	4.30
SEM		0.01	0.36	0.02	0.38	0.02	0.36	0.03	0.33	0.01	0.31
D.I.	Sodium	0.23	5.23	0.22	5.13	0.26	5.73	0.27	5.72	0.32	5.74
I.W.	Cromoglycate	0.12	4.57	0.12	4.47	0.20	5.93	0.22	5.56	0.21	5.11
A.G.+		0.16	2.95	0.14	3.02	0.23	3.35	0.19	3.68	0.20	3.56
K.C.+		0.17	3.93	0.17	3.97	0.29	4.15	0.24	4.23	0.22	4.19
R.G.+		0.13	3.45	0.13	3.63	0.36	3.91	0.23	3.43	0.21	3.40
N.T.+		0.13	4.01	0.13	4.01	0.17	4.31	0.19	4.25	0.18	4.23
Mean		0.16	4.02	0.15	4.04	0.25	4.56	0.22	4.48	0.22	4.37
SEM		0.01	0.33	0.01	0.29	0.02	0.42	0.01	0.39	0.02	0.37

+ Subjects with upper respiratory tract infection

B, before pre-treatment; A, after saline, ipratropium, bupivacaine or sodium cromoglycate

Raw ($kPal^{-S}s$); V_{tg} (l)

* Values significantly different from saline pre-treatment at that time ($p < 0.05$)

TABLE LXIII Effect of inhaled prostaglandin $F_{2\alpha}$ on Raw and V_{tg} in normal subjects (N = 5)

Subjects	Pre-treatment	Baseline B Raw	Baseline B V_{tg}	Baseline A Raw	Baseline A V_{tg}	Change in Raw and V_{tg} after prostaglandin (0.5 g/l) 1 min Raw	1 min V_{tg}	5 min Raw	5 min V_{tg}
K.C.	Saline	0.14	2.30	0.17	2.45	0.20	3.29	0.23	2.94
D.I.		0.18	5.56	0.18	5.78	0.22	5.65	0.28	5.55
I.W.		0.15	5.39	0.15	5.27	0.18	5.80	0.37	6.50
K.P.		0.10	4.20	0.15	3.71	0.23	4.02	0.20	4.32
A.G.		0.21	2.89	0.18	2.97	0.30	4.14	0.20	3.96
Mean		0.16	4.07	0.17	4.04	0.23	4.58	0.26	4.65
SEM		0.01	0.65	0.01	0.64	0.02	0.49	0.03	0.62
K.C.	Ipratropium	0.11	2.93	0.08	2.76	0.08	2.81	0.07	3.38
D.I.		0.15	5.94	0.14	5.97	0.17	5.46	0.26	4.72
I.W.		0.22	6.18	0.18	5.62	0.20	5.20	0.30	5.76
K.P.		0.22	4.12	0.14	4.29	0.20	4.00	0.23	3.59
A.G.		0.13	3.02	0.07	3.28	0.11	3.33	0.14	3.99
Mean		0.17	4.44	0.12	4.38	0.15	4.16*	0.20	4.29
SEM		0.02	0.69	0.02	0.63	0.02	0.52	0.04	0.43
K.C.	Bupivacaine	0.13	2.37	0.11	2.63	0.17	3.25	0.17	3.41
D.I.		0.20	5.88	0.20	5.72	0.21	5.90	0.32	5.81
I.W.		0.14	5.32	0.14	5.38	0.23	5.10	0.41	5.83
K.P.		0.25	4.03	0.25	4.03	0.39	4.08	0.35	4.26
A.G.		0.15	2.65	0.17	2.44	0.22	3.12	0.29	3.30
Mean		0.17	4.05	0.17	4.04	0.24	4.29	0.31	4.52
SEM		0.02	0.69	0.02	0.67	0.03	0.53	0.04	0.55

B, before pre-treatment; A, after saline, ipratropium or bupivacaine

Raw ($kPal^{-s}S$); V_{tg} (l)

* Values significantly different from saline pre-treatment at that time ($p < 0.05$)

TABLE LXIV Effect of inhaled cigarette smoke on Raw and V_{tg} following ipratropium, bupivacaine or saline in normal subjects (N = 8)

Subjects	Pre-treatment	Baseline B Raw	Baseline B V_{tg}	Baseline A Raw	Baseline A V_{tg}	Change in Raw and V_{tg} after cigarette smoke 2 min Raw	2 min V_{tg}
R.J.	Saline	0.15	3.21	0.14	3.20	0.17	3.56
K.R.		0.23	2.39	0.22	2.27	0.26	2.20
M.S.		0.15	2.01	0.14	1.81	0.19	1.91
A.L.		0.11	3.13	0.13	2.71	0.15	3.66
W.F.		0.08	6.28	0.09	5.14	0.13	5.52
Y.I.		0.35	3.33	0.30	3.22	0.34	3.38
L.F.		0.35	2.78	0.43	2.21	0.45	2.32
I.W.		0.19	5.00	0.19	4.86	0.23	5.44
Mean		0.20	3.51	0.20	3.17	0.24	3.49
SEM		0.03	0.50	0.03	0.43	0.03	0.49
R.J.	Sodium	0.11	3.08	0.09	3.01	0.14	2.98
K.R.	Cromoglycate	0.15	2.67	0.13	2.79	0.24	2.18
M.S.		0.11	2.56	0.14	1.99	0.18	2.04
A.L.		0.11	3.97	0.11	3.60	0.19	3.51
W.F.		0.09	5.00	0.14	5.16	0.19	4.99
Y.I.		0.29	3.43	0.25	3.05	0.25	3.09
L.F.		0.27	2.56	0.38	2.47	0.56	2.27
I.W.		0.17	5.02	0.17	4.86	0.21	4.64
Mean		0.16	3.53	0.17	3.36	0.24	3.21
SEM		0.02	0.36	0.03	0.39	0.04	0.39
R.J.	Ipratropium	0.10	2.94	0.08	3.04	0.08	3.10
K.R.		0.20	2.73	0.14	2.24	0.16	1.95
M.S.		0.16	1.98	0.10	1.85	0.09	1.91
A.L.		0.12	3.27	0.19	3.30	0.09	3.17
W.F.		0.15	5.31	0.11	5.55	0.12	5.12
Y.I.		0.37	3.08	0.28	3.11	0.34	3.32
L.F.		0.27	2.66	0.19	2.87	0.15	2.59
I.W.		0.15	5.44	0.17	4.56	0.16	4.97
Mean		0.19	3.42	0.15	3.31	0.14*	3.26
SEM		0.03	0.44	0.02	0.42	0.02	0.43
R.J.	Bupivacaine	0.11	3.22	0.13	3.14	0.17	3.22
K.R.		0.19	2.39	0.19	2.95	0.24	2.50
M.S.		0.15	1.93	0.16	1.87	0.20	1.96
A.L.		0.14	2.78	0.12	3.32	0.16	3.41
W.F.		0.12	5.57	0.14	5.20	0.15	5.57
Y.I.		0.30	3.30	0.30	3.31	0.38	3.42
L.F.		0.32	2.74	0.37	2.25	0.53	2.65
I.W.		0.20	5.47	0.20	5.12	0.21	5.24
Mean		0.19	3.42	0.20	3.39	0.25	3.49
SEM		0.02	0.48	0.03	0.42	0.04	0.45

B, before pre-treatment; A, after saline, sodium cromoglycate, ipratropium or bupivacaine

Raw ($kPal^{-S}S$); V_{tg} (l)

* Values significantly different from saline pre-treatment at 2 min ($p < 0.05$)

TABLE LXV Effect of exercise on FEV_1 following ipratropium, atropine or saline in asthmatic patients (N = 9)

Patient No	Baseline FEV_1 (l)						Change in FEV_1 after exercise								
	B			A			5 min			10 min			20 min		
	Sal	IB	AS	Sal	IB	AS	Sal	IB	AS	Sal	IB	AS	Sal	IB	AS
1	2.18	2.32		2.23	2.68		-0.70	-0.17		-0.56	-0.23		-0.09	-0.02	
2	2.63	2.61		2.61	3.06		-0.63	-0.21		-0.54	-0.11		-0.58	-0.07	
3	2.75	2.73		2.88	3.13		-1.31	-0.37		-1.33	-0.38		-0.53	-0.20	
4	2.03	2.08	2.03	1.95	2.68	2.71	-0.90	-0.89	-0.86	-0.74	-0.85	-1.38	-0.32	-0.47	-0.76
5	3.01	2.96	2.70	3.01	3.33	3.29	-1.78	-1.95	-1.64	-1.99	-2.21	-1.95	-1.43	-1.81	-1.66
6	2.03	2.10	2.23	2.01	2.48	2.53	-0.47	-0.77	-1.00	-0.66	-0.73	-1.32	-0.46	-0.33	-0.80
7	4.56	4.51		4.73	4.62		-1.45	+0.02		-1.28	+0.05		-0.89	-0.03	
8	3.26	3.34		3.34	3.56		-0.66	-0.23		-0.67	-0.27		-0.22	+0.03	
9	3.26	3.90	3.80	3.85	4.40	4.50	-1.17	-2.86	-2.19	-1.56	-3.06	-3.11	-1.51	-2.37	-1.99
Mean	2.92	2.95	2.69	2.95	3.32	3.25	-0.99	-0.82	-1.42	-1.03	-0.86	-1.94	-0.67	-0.58	-1.30
SEM	0.28	0.27	0.39	0.30	0.25	0.44	0.14	0.32	0.30	0.17	0.35	0.41	0.16	0.29	0.30

B, before pre-treatment; A, after saline (Sal), ipratropium bromide (IB), or atropine sulphate (AS)

TABLE LXVI Effect of exercise on FEV_1 following saline in asthmatic patients (N = 13)

Patient No	Baseline FEV_1 (l) B	Baseline FEV_1 (l) A	Absolute values for FEV_1 after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	3.51	3.52	3.19	2.25	2.65	2.80	2.90
2	2.52	2.52	2.70	1.50	1.26	1.68	1.90
3	2.69	2.93	2.69	2.38	2.32	2.49	2.55
4	2.85	2.68	1.57	1.47	1.31	1.31	1.41
5	4.86	4.75	3.54	3.54	4.01	4.35	4.38
6	3.13	3.19	3.41	2.91	2.54	2.83	2.95
7	3.20	3.20	2.75	2.10	2.50	2.95	3.00
8	2.87	3.14	0.91	0.94	1.28	1.24	1.14
Mean	3.20	3.24	2.59	2.14	2.23	2.46	2.53
SEM	0.26	0.24	0.32	0.30	0.33	0.36	0.37
Non-responders							
9	3.08	3.15	2.03	1.93	1.86	2.44	2.06
10	3.25	3.25	1.79	1.66	1.42	1.66	1.73
11	3.68	3.63	2.96	2.52	2.62	2.79	2.81
12	1.67	1.71	1.51	1.41	1.31	1.41	1.31
13	1.86	1.75	1.19	1.30	1.15	1.20	1.24
Mean	2.71	2.69	1.90	1.76	1.67	1.90	1.83
SEM	0.40	0.40	0.30	0.22	0.26	0.31	0.29

B, before pre-treatment; A, after saline

TABLE LXVII Effect of exercise on FEV_1 following sodium cromoglycate in asthmatic patients (N = 13)

Patient No	Baseline FEV_1 (1) B	Baseline FEV_1 (1) A	Absolute values for FEV_1 after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	3.11	2.95	2.41	2.34	2.51	2.98	3.05
2	2.28	2.39	2.82	2.72	2.65	2.59	2.69
3	2.74	2.91	2.88	2.40	2.64	2.77	2.76
4	2.60	2.40	2.74	1.96	2.03	2.05	2.33
5	5.07	4.87	4.97	4.77	4.74	4.71	4.81
6	3.21	3.48	3.61	3.55	3.25	3.31	3.35
7	3.43	3.67	2.27	2.55	2.92	3.09	3.23
8	2.84	3.38	3.55	1.99	1.93	2.71	3.15
Mean	3.16	3.23	3.16	2.78	2.83	3.03	3.17
SEM	0.30	0.28	0.31	0.33	0.31	0.27	0.26
Non-responders							
9	3.30	3.74	4.11	3.61	3.71	3.84	3.84
10	3.28	2.88	3.04	3.05	3.01	2.88	2.96
11	3.38	3.38	3.38	3.28	3.31	3.51	3.45
12	1.57	1.67	1.86	1.61	1.47	1.57	1.71
13	1.63	1.85	1.28	1.28	1.31	1.34	1.38
Mean	2.63	2.65	2.73	2.57	2.56	2.63	2.67
SEM	0.42	0.40	0.51	0.47	0.49	0.50	0.48

B, before pre-treatment; A, after sodium cromoglycate

TABLE LXVIII Effect of exercise on FEV_1 following ipratropium in asthmatic patients (N = 13)

Patient No	Baseline FEV_1 (1) B	Baseline FEV_1 (1) A	Absolute values for FEV_1 after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	2.92	3.44	3.21	2.89	2.99	3.14	3.39
2	2.68	2.74	2.81	2.34	2.24	2.24	2.24
3	2.80	2.93	2.87	2.83	2.93	2.97	2.90
4	2.89	3.19	3.36	3.19	3.16	3.16	3.19
5	4.80	5.24	4.54	4.46	4.64	4.84	5.00
6	3.51	3.47	3.61	3.37	3.20	3.23	3.20
7	3.51	3.45	2.36	2.36	3.01	3.01	3.21
8	2.34	3.10	2.63	1.60	1.48	1.36	1.52
Mean	3.14	3.42	3.17	2.88	2.96	2.99	3.08
SEM	0.27	0.27	0.24	0.30	0.32	0.35	0.35
Non-responders							
9	3.19	4.20	2.28	2.15	2.12	2.22	2.55
10	3.23	3.43	2.05	2.00	1.98	1.98	2.03
11	2.83	3.69	3.03	2.71	2.90	3.12	3.22
12	1.58	1.91	1.65	1.21	1.08	1.13	1.31
13	2.04	2.03	1.47	1.47	1.41	1.51	1.51
Mean	2.54	3.00	2.10	1.91	1.90	1.99	2.12
SEM	0.32	0.45	0.27	0.26	0.31	0.34	0.35

B, before pre-treatment; A, after ipratropium

TABLE LXIX Effect of exercise on FEV_1 following ipratropium plus sodium cromoglycate in asthmatic patients (N = 13)

Patient No	Baseline FEV_1 (l)		Absolute values for FEV_1 after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
Responders							
1	3.24	3.69	3.39	3.23	3.33	3.46	3.43
2	2.49	2.76	2.83	2.76	2.60	2.76	2.76
3	2.68	2.78	2.68	2.68	2.64	2.64	2.68
4	2.23	3.04	3.24	3.35	3.15	3.28	3.23
5	4.95	5.05	5.36	5.29	5.12	5.09	5.29
6	3.31	3.43	3.55	3.52	3.32	3.35	3.35
7	3.11	3.69	2.30	2.47	2.77	3.08	3.18
8	3.35	3.28	3.05	2.64	3.28	3.41	3.45
Mean	3.15	3.44	3.30	3.24	3.28	3.38	3.42
SEM	0.29	0.26	0.33	0.32	0.28	0.27	0.29
Non-responders							
9	2.57	4.03	4.02	3.72	3.70	3.81	3.81
10	3.22	3.59	3.73	3.76	3.69	3.73	3.69
11	3.53	3.95	4.05	4.02	3.90	4.12	3.92
12	1.94	2.14	2.58	2.31	2.38	2.48	2.18
13	1.47	1.67	1.34	1.27	1.44	1.27	1.24
Mean	2.54	3.03	3.14	3.02	3.02	3.08	2.97
SEM	0.38	0.48	0.52	0.53	0.48	0.53	0.54

B, before pre-treatment; A, after ipratropium plus sodium cromoglycate

TABLE LXX Effect of exercise on FVC following saline in asthmatic patients (N = 13)

Patient No	Baseline FVC (l) B	Baseline FVC (l) A	Absolute values for FVC after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	4.40	4.40	4.18	3.74	4.18	4.42	4.30
2	3.28	3.28	3.20	2.10	2.45	2.73	2.90
3	3.56	3.69	3.31	3.28	3.31	3.26	3.46
4	3.58	3.48	2.09	2.44	2.24	2.08	2.44
5	6.17	6.10	4.96	5.23	5.66	5.90	5.80
6	3.82	3.93	4.17	4.08	3.53	3.88	3.67
7	4.30	4.35	4.20	3.75	4.45	4.50	4.45
8	4.20	4.17	1.41	1.39	2.30	2.49	2.28
Mean	4.16	4.17	3.44	3.25	3.51	3.66	3.66
SEM	0.32	0.30	0.42	0.43	0.43	0.45	0.41
Non-responders							
9	6.09	6.09	4.33	3.99	3.89	4.94	4.48
10	4.16	4.33	3.21	2.94	2.69	3.01	3.05
11	5.09	5.09	4.94	4.64	4.33	4.91	4.50
12	3.41	3.55	2.51	2.53	2.64	2.95	2.96
13	3.83	3.73	2.79	2.70	2.60	2.82	3.01
Mean	4.52	4.55	3.56	3.36	3.23	3.73	3.60
SEM	0.48	0.46	0.46	0.41	0.37	0.49	0.36

B, before pre-treatment; A, after saline

TABLE LXXI Effect of exercise on FVC following sodium cromoglycate in asthmatic patients (N = 13)

Patient No	Baseline FVC (l)		Absolute values for FVC after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
Responders							
1	4.15	4.08	4.02	3.75	4.02	4.38	4.38
2	2.99	2.92	3.19	3.17	3.09	3.11	3.17
3	3.38	3.62	3.52	3.11	3.26	3.38	3.43
4	3.55	3.21	3.25	2.67	2.91	2.88	3.20
5	5.78	5.68	5.34	5.78	5.74	5.97	5.84
6	3.98	4.08	4.32	4.25	4.02	4.02	4.05
7	4.70	4.79	3.50	4.18	4.82	4.92	4.87
8	3.96	4.40	4.57	2.81	3.15	3.92	4.43
Mean	4.06	4.09	3.96	3.71	3.88	4.07	4.17
SEM	0.31	0.31	0.26	0.36	0.35	0.36	0.32
Non-responders							
9	5.46	6.49	6.66	6.44	6.44	6.58	6.94
10	4.40	4.20	4.43	4.33	4.25	4.20	4.29
11	4.72	4.84	5.05	5.12	4.87	5.09	4.94
12	3.11	3.28	3.31	3.15	2.96	3.11	3.40
13	3.53	3.70	2.67	2.99	2.91	3.02	3.12
Mean	4.24	4.46	4.42	4.41	4.29	4.40	4.54
SEM	0.42	0.56	0.70	0.64	0.66	0.66	0.68

B, before pre-treatment; A, after sodium cromoglycate

TABLE LXXII Effect of exercise on FVC following ipratropium in asthmatic patients (N = 13)

Patient No	Baseline FVC (1) B	Baseline FVC (1) A	Absolute values for FVC after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	4.38	4.17	4.33	4.32	4.47	4.54	4.69
2	3.30	3.13	3.10	3.05	3.25	3.05	3.13
3	3.71	3.67	3.81	3.64	3.73	3.78	3.61
4	3.80	3.59	3.63	3.88	3.59	3.70	3.70
5	5.88	6.05	5.74	5.78	5.81	5.96	6.05
6	4.02	3.98	4.21	4.01	3.88	3.93	3.95
7	4.55	4.59	4.15	4.25	4.75	4.75	4.72
8	3.34	3.99	3.30	3.02	2.34	2.24	2.39
Mean	4.10	4.09	4.03	3.99	3.98	3.99	4.03
SEM	0.29	0.31	0.29	0.31	0.37	0.40	0.40
Non-responders							
9	5.98	6.88	4.33	4.12	4.37	4.70	5.04
10	4.43	4.43	3.49	3.51	3.59	3.63	3.56
11	4.62	4.82	4.62	4.62	4.75	4.72	4.79
12	3.12	3.83	3.12	2.72	2.57	2.69	2.97
13	3.65	3.83	3.06	3.21	3.28	3.40	3.41
Mean	4.34	4.71	3.72	3.64	3.71	3.83	3.95
SEM	0.48	0.56	0.32	0.33	0.39	0.39	0.41

B, before pre-treatment; A, after ipratropium

TABLE LXXIII Effect of exercise on FVC following ipratropium plus sodium cromoglycate in asthmatic patients (N = 13)

Patient No	Baseline FVC (l) B	Baseline FVC (l) A	Absolute values for FVC after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	4.31	4.59	4.41	4.46	4.32	4.51	4.42
2	3.09	3.31	3.33	3.29	3.23	2.99	3.03
3	3.43	3.38	3.50	3.40	3.33	3.39	3.46
4	2.98	3.65	3.89	3.99	3.82	3.94	3.79
5	5.86	5.99	6.08	6.12	6.13	6.06	6.23
6	3.97	4.04	4.20	4.18	4.00	4.00	4.08
7	4.77	4.80	4.04	4.55	4.64	4.91	4.77
8	4.52	4.39	3.98	3.98	4.12	4.12	4.30
Mean	4.09	4.26	4.18	4.25	4.20	4.24	4.26
SEM	0.34	0.31	0.30	0.31	0.32	0.33	0.34
Non-responders							
9	5.08	6.62	6.60	6.30	6.30	6.41	6.69
10	4.43	4.42	4.43	4.64	4.74	4.72	4.74
11	4.84	4.98	5.15	5.12	5.22	5.12	5.09
12	3.50	3.75	4.29	4.03	3.98	4.01	3.63
13	3.41	3.58	3.06	3.10	3.18	3.10	3.23
Mean	4.27	4.63	4.71	4.64	4.68	4.67	4.68
SEM	0.34	0.54	0.58	0.53	0.53	0.55	0.61

B, before pre-treatment; A, after ipratropium plus sodium cromoglycate

TABLE LXXIV Effect of exercise on MMEF following saline in asthmatic patients (N = 13)

Patient No	Baseline MMEF (1 sec^{-1})		Absolute values for MMEF after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
Responders							
1	2.43	2.51	1.62	1.41	2.10	2.20	2.21
2	2.02	2.12	2.56	1.06	1.21	1.41	1.88
3	2.16	2.46	2.38	1.98	1.62	2.08	2.06
4	3.06	2.47	1.18	0.88	0.80	0.95	0.79
5	5.21	4.75	3.20	2.50	2.92	3.45	3.74
6	3.32	3.56	3.49	3.53	2.50	2.87	3.14
7	2.58	2.63	1.21	1.31	1.31	1.72	2.01
8	1.91	2.33	0.50	0.66	0.71	0.55	0.51
Mean	2.84	2.85	2.02	1.67	1.65	1.90	2.04
SEM	0.38	0.30	0.37	0.34	0.28	0.34	0.38
Non-responders							
9	1.37	1.44	0.91	1.00	0.95	1.19	0.95
10	2.95	2.63	0.98	0.91	0.77	0.88	0.94
11	3.23	2.97	2.02	1.53	1.60	1.82	1.74
12	0.78	0.85	1.21	0.82	0.71	0.69	0.70
13	0.75	0.78	0.62	0.62	0.50	0.57	0.57
Mean	1.82	1.73	1.15	0.98	0.91	1.03	0.98
SEM	0.53	0.45	0.24	0.15	0.19	0.22	0.20

B, before pre-treatment; A, after saline

TABLE LXXV Effect of exercise on MMEF following sodium cromoglycate in asthmatic patients (N = 13)

Patient No	Baseline MMEF (1 sec^{-1}) B	A	Absolute values for MMEF after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	2.63	2.21	1.50	1.41	1.73	2.02	2.18
2	1.75	2.41	3.56	2.87	3.11	2.81	3.01
3	2.71	3.09	2.61	2.22	2.82	2.76	2.60
4	1.72	1.87	2.14	1.47	1.37	1.49	1.77
5	5.05	5.16	5.53	4.70	4.78	5.47	5.16
6	3.24	3.89	4.18	4.30	3.65	3.65	3.88
7	2.53	3.15	1.51	1.51	1.52	1.80	2.07
8	2.03	2.95	3.21	1.46	1.06	1.84	2.44
Mean	2.71	3.04	3.03	2.49	2.50	2.73	2.89
SEM	0.38	0.36	0.49	0.47	0.46	0.46	0.40
Non-responders							
9	1.79	1.90	2.39	1.77	2.05	2.03	2.20
10	2.42	2.00	2.00	2.06	2.14	1.95	2.15
11	2.66	2.50	2.64	2.28	2.52	2.68	2.71
12	0.72	0.71	0.99	0.88	0.70	0.80	0.77
13	0.83	0.86	0.63	0.63	0.60	0.61	0.61
Mean	1.68	1.50	1.73	1.52	1.60	1.61	1.69
SEM	0.40	0.36	0.39	0.33	0.40	0.39	0.42

B, before pre-treatment; A, after sodium cromoglycate

TABLE LXXVI Effect of exercise on MMEF following ipratropium in asthmatic patients (N = 13)

Patient No	Baseline MMEF (l sec-1) B	A	Absolute values for MMEF after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	1.90	3.33	2.50	1.75	2.15	2.23	2.73
2	2.55	3.42	3.20	1.91	1.72	1.81	1.83
3	2.48	3.16	2.53	2.43	2.85	2.88	2.89
4	2.66	4.07	4.49	3.19	3.56	3.70	3.99
5	4.47	5.49	4.80	3.61	4.33	4.30	5.04
6	4.23	3.79	5.14	3.82	3.49	3.28	3.55
7	3.01	3.04	1.57	1.19	1.86	2.01	2.27
8	1.65	2.79	2.34	0.99	0.87	0.78	0.84
Mean	2.81	3.59	3.32	2.36	2.60	2.62	2.89
SEM	0.35	0.30	0.47	0.38	0.41	0.40	0.46
Non-responders							
9	1.51	2.20	1.12	1.02	0.87	1.06	1.17
10	2.03	2.13	1.15	0.97	0.95	1.00	1.08
11	1.78	3.16	2.07	1.82	2.04	2.34	2.44
12	0.72	0.78	0.79	0.59	0.52	0.60	0.64
13	1.17	1.12	0.65	0.61	0.61	0.55	0.67
Mean	1.34	1.74	1.16	1.00	1.00	1.11	1.20
SEM	0.24	0.43	0.25	0.22	0.27	0.32	0.33

B, before pre-treatment; A, after ipratropium

TABLE LXXVII Effect of exercise on MMEF following ipratropium plus sodium cromoglycate in asthmatic patients (N = 13)

Patient No	Baseline MMEF (l sec^{-1}) B	A	Absolute values for MMEF after exercise 2 min	5 min	10 min	15 min	20 min
Responders							
1	2.49	3.80	2.76	2.48	2.54	2.99	2.93
2	2.23	3.50	3.91	2.99	2.93	2.49	2.69
3	2.41	3.95	3.20	3.15	3.14	3.31	3.43
4	1.90	3.68	3.77	4.06	3.44	3.83	3.91
5	5.06	5.38	5.92	5.87	5.64	5.64	5.90
6	3.54	3.79	4.02	4.12	3.60	3.59	3.63
7	2.38	2.98	1.07	1.21	1.46	1.76	2.18
8	2.64	3.24	3.79	2.49	3.12	3.43	3.32
Mean	2.78	3.77	3.55	3.30	3.23	3.38	3.50
SEM	0.35	0.25	0.48	0.49	0.42	0.40	0.39
Non-responders							
9	1.18	2.28	2.30	1.82	2.20	2.28	2.28
10	2.48	3.26	4.13	3.38	3.17	3.06	3.22
11	2.83	3.53	3.86	3.16	3.12	3.62	3.51
12	0.97	1.17	1.34	1.24	1.31	1.43	1.26
13	0.70	0.85	0.64	0.59	0.63	0.59	0.59
Mean	1.53	2.09	2.45	2.04	2.09	2.20	2.17
SEM	0.43	0.54	0.68	0.54	0.50	0.54	0.56

B, before pretreatment; A, after ipratropium plus sodium cromoglycate

TABLE LXXVIII Effect of exercise on FEV_1 following FPL57787 or placebo in asthmatic patients (N = 10)

Patient No	Pre-drug	2 hr Post-drug	Absolute values for FEV_1 after exercise				
			2 min	5 min	10 min	15 min	20 min
		PLACEBO					
1	4.45	4.35	4.35	3.41	3.08	3.05	3.18
2	3.72	3.85	2.21	1.71	1.97	1.91	2.08
3	2.85	2.56	2.34	2.04	1.97	2.21	2.31
4	3.85	4.49	3.15	1.91	1.87	1.82	2.01
5	2.81	3.08	1.98	1.64	1.89	1.92	2.01
6	3.48	3.28	3.18	2.41	2.44	2.81	2.78
7	2.98	2.91	2.01	1.99	2.41	2.53	2.61
8	2.58	2.58	1.77	1.64	1.67	1.54	1.97
9	4.85	5.10	3.88	2.76	2.24	2.73	2.44
10	1.76	1.84	1.77	1.12	1.02	1.04	0.94
Mean	3.33	3.40	2.66	2.06	2.06	2.16	2.23
SEM	0.29	0.32	0.29	0.21	0.17	0.20	0.19
		FPL57787					
1	4.79	5.02	5.36	5.02	4.95	4.79	5.02
2	3.58	4.05	2.85	2.81	2.88	3.01	3.01
3	2.24	2.31	2.38	2.01	1.94	1.91	1.98
4	4.15	5.05	3.75	3.01	3.68	3.95	4.20
5	2.38	3.03	2.95	2.51	2.68	2.81	2.95
6	3.63	3.55	3.55	3.18	3.26	3.45	3.38
7	2.90	2.85	2.39	2.54	2.51	2.61	2.88
8	2.95	2.95	2.74	2.54	2.81	2.44	2.90
9	4.35	4.97	4.15	3.21	3.75	3.88	4.12
10	1.82	2.28	2.08	1.87	1.91	1.87	1.87
Mean	3.28	3.61	3.22	2.87	3.04	3.07	3.23
SEM	0.31	0.35	0.32	0.28	0.29	0.30	0.31

TABLE LXXIX Effect of exercise on FVC following FPL57787 or placebo in asthmatic patients (N = 10)

Patient No	Pre-drug	2 hr Post-drug	Absolute values for FVC after exercise				
			2 min	5 min	10 min	15 min	20 min
		PLACEBO					
1	5.36	5.29	5.52	5.02	4.87	4.75	4.89
2	5.29	5.59	4.05	3.31	3.98	4.08	4.28
3	4.02	3.88	4.02	3.62	3.62	3.92	3.88
4	6.89	7.00	5.96	4.02	4.35	4.79	5.12
5	4.07	4.44	3.55	3.08	3.56	3.63	3.75
6	4.52	4.69	4.25	4.25	4.22	4.32	4.42
7	3.38	3.41	2.78	3.01	3.28	3.30	3.35
8	3.35	3.30	3.05	2.84	2.88	2.61	3.11
9	5.69	5.76	4.79	4.80	4.02	4.54	4.22
10	3.65	3.58	3.81	2.81	2.84	2.64	2.60
Mean	4.62	4.69	4.18	3.68	3.76	3.86	3.96
SEM	0.37	0.38	0.32	0.26	0.21	0.25	0.25
		FPL57787					
1	5.56	5.52	5.66	5.59	5.66	5.52	5.72
2	5.35	5.62	4.85	4.82	5.09	5.12	5.32
3	3.95	3.62	4.02	3.88	3.48	3.48	3.51
4	6.89	7.36	6.88	6.13	6.75	7.20	7.16
5	3.93	4.39	4.32	4.05	4.19	4.35	4.35
6	4.79	4.65	4.82	4.75	4.74	4.75	4.85
7	3.36	3.45	3.25	3.35	3.31	3.35	3.40
8	3.65	3.72	3.45	3.11	3.58	3.35	3.68
9	5.62	5.59	5.25	4.87	5.79	5.75	5.79
10	3.62	3.82	3.95	3.75	3.51	3.55	3.65
Mean	4.67	4.77	4.64	4.43	4.61	4.64	4.74
SEM	0.36	0.39	0.35	0.31	0.38	0.40	0.39

TABLE LXXX Effect of exercise on MMEF following FPL57787 or placebo in asthmatic patients (N = 10)

Patient No	Pre-drug	2 hr Post-drug	Absolute values for MMEF after exercise				
			2 min	5 min	10 min	15 min	20 min
		PLACEBO					
1	4.81	5.04	3.97	2.18	1.70	1.74	1.93
2	2.64	2.68	1.21	0.90	0.93	0.96	0.95
3	2.06	1.81	1.28	1.12	0.98	1.09	1.39
4	1.89	2.59	1.56	1.02	0.87	0.87	1.01
5	1.87	2.19	1.09	0.91	0.99	0.97	1.04
6	2.85	2.39	2.56	1.69	1.49	1.84	1.79
7	3.72	3.79	1.52	1.28	1.93	2.19	2.50
8	2.57	2.38	1.00	0.94	1.17	0.84	1.21
9	4.94	6.10	3.42	1.59	1.30	1.78	1.48
10	0.78	0.88	0.68	0.40	0.42	0.42	0.35
Mean	2.81	2.98	1.83	1.20	1.18	1.27	1.36
SEM	0.42	0.49	0.35	0.16	0.14	0.18	0.19
		FPL57787					
1	5.85	7.32	10.35	6.58	5.66	5.56	6.02
2	2.68	2.96	1.62	1.51	1.48	1.65	1.90
3	1.24	1.51	1.36	1.06	1.06	0.98	1.00
4	2.37	3.27	1.85	1.17	1.91	2.11	2.33
5	1.36	2.08	1.89	1.43	1.69	1.79	1.91
6	2.92	3.00	2.88	2.26	2.28	2.64	2.68
7	3.38	2.79	1.87	2.34	2.03	2.16	3.25
8	3.07	3.09	3.83	2.37	2.63	2.17	2.68
9	5.66	5.62	4.35	2.35	2.76	3.01	3.51
10	0.77	1.24	1.20	0.89	1.07	1.09	1.01
Mean	2.93	3.29	3.12	2.20	2.26	2.32	2.63
SEM	0.54	0.59	0.87	0.52	0.42	0.41	0.46

TABLE LXXXI Effect of exercise on FEV_1 following saline in asthmatic patients (N = 10)

Patient No	Baseline FEV_1 (l) B	Baseline FEV_1 (l) A	Absolute values for FEV_1 after exercise 2 min	5 min	10 min	15 min	20 min
1	3.72	3.78	3.21	2.41	2.44	2.68	2.88
2	5.35	5.29	4.46	4.04	4.19	4.17	4.25
3	2.32	2.51	1.67	1.34	1.34	1.41	1.27
4	2.63	2.53	2.34	1.77	1.51	1.44	1.47
5	3.01	3.03	1.89	1.77	2.11	2.31	2.48
6	3.52	3.38	2.96	2.54	2.71	2.78	3.03
7	2.84	3.25	2.84	2.24	2.64	2.51	2.75
8	2.89	2.88	2.08	2.01	2.13	2.14	2.34
9	2.96	2.88	2.68	2.21	2.44	2.66	2.58
10	1.76	1.64	1.14	1.07	1.20	1.17	1.15
Mean	3.10	3.12	2.53	2.14	2.27	2.33	2.42
SEM	0.30	0.30	0.29	0.26	0.27	0.28	0.30

B, before pre-treatment; A, after saline

TABLE LXXXII Effect of exercise on FEV_1 following clemastine in asthmatic patients (N = 10)

Patient No	Baseline FEV_1 (l)		Absolute values for FEV_1 after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
1	3.58	3.64	3.35	3.12	2.31	2.68	2.70
2	5.35	5.51	5.62	4.70	4.20	4.16	4.30
3	2.07	2.58	2.38	1.87	1.96	2.00	2.16
4	2.78	3.08	3.01	2.85	2.33	2.98	3.03
5	3.11	3.05	2.91	2.75	2.23	2.64	2.88
6	3.62	3.35	2.95	2.81	2.85	3.11	3.08
7	3.08	3.21	3.68	2.43	3.01	3.01	3.08
8	2.91	3.25	3.00	2.51	2.64	2.54	2.58
9	2.91	2.91	2.61	1.84	2.49	2.61	2.51
10	2.31	2.31	1.94	1.64	1.67	1.64	1.64
Mean	3.17	3.29	3.14	2.65	2.57	2.74	2.80
SEM	0.29	0.27	0.31	0.28	0.22	0.21	0.22

B, before pre-treatment; A, after clemastine

TABLE LXXXIII Effect of exercise on FEV_1 following cimetidine in asthmatic patients (N = 10)

Patient No	Baseline FEV_1 (l)		Absolute values for FEV_1 after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
1	4.02	3.82	3.85	3.06	3.31	3.35	3.68
2	5.62	5.84	5.72	5.07	5.07	5.15	5.12
3	2.31	2.41	1.91	1.71	1.84	1.94	2.04
4	2.84	2.78	2.41	2.08	1.98	2.01	2.14
5	2.54	2.98	2.16	2.11	2.61	2.64	2.69
6	3.52	3.45	2.95	2.81	2.68	3.11	3.08
7	2.63	2.85	2.88	2.14	2.53	2.51	2.54
8	2.88	2.48	2.54	2.28	2.43	2.28	2.79
9	2.64	2.34	2.34	1.81	2.08	2.11	2.34
10	1.92	1.77	1.36	1.27	1.40	1.27	1.40
Mean	3.10	3.07	2.81	2.43	2.59	2.64	2.78
SEM	0.34	0.36	0.38	0.33	0.32	0.34	0.32

B, before pre-treatment; A, after cimetidine

TABLE LXXXVI Effect of exercise on FVC following cimetidine in asthmatic patients (N = 10)

Patient No	Baseline FVC (1) B	Baseline FVC (1) A	Absolute values for FVC after exercise 2 min	5 min	10 min	15 min	20 min
1	4.99	4.85	4.85	4.32	4.59	4.62	4.82
2	7.77	7.65	7.45	7.50	7.45	7.39	7.51
3	3.28	3.18	2.95	2.64	2.81	3.08	3.01
4	3.51	3.41	3.25	3.05	2.91	2.88	3.05
5	3.51	3.65	3.25	3.13	3.75	3.72	3.82
6	4.75	4.34	4.22	4.12	4.62	4.42	4.45
7	3.88	3.82	3.92	3.25	3.65	3.72	3.88
8	4.42	3.83	3.97	3.77	4.22	3.93	4.42
9	3.65	3.55	3.25	3.01	3.36	3.38	3.62
10	2.81	2.64	2.04	1.91	2.11	2.01	2.06
Mean	4.26	4.09	3.91	3.67	3.95	3.91	4.06
SEM	0.44	0.44	0.46	0.48	0.46	0.45	0.46

B, before pre-treatment; A, after cimetidine

TABLE LXXXV Effect of exercise on FVC following clemastine in asthmatic patients (N = 10)

Patient No	Baseline FVC (l)		Absolute values for FVC after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
1	4.05	4.32	4.25	3.61	3.14	3.51	3.58
2	7.78	7.82	7.72	7.39	7.05	7.05	7.22
3	3.20	3.25	3.15	2.90	2.95	3.06	3.10
4	3.55	3.65	3.58	3.21	3.68	3.68	3.66
5	3.77	3.68	3.65	3.68	3.46	3.82	3.72
6	4.57	4.45	4.39	4.45	4.28	4.45	4.45
7	3.75	3.92	3.98	3.41	3.85	3.88	3.82
8	4.69	4.79	4.49	4.15	4.19	4.42	4.32
9	3.58	3.58	3.40	3.18	3.54	3.51	3.58
10	3.11	3.11	2.83	2.64	2.68	2.78	2.68
Mean	4.20	4.23	4.14	3.86	3.88	4.02	4.02
SEM	0.43	0.43	0.43	0.43	0.39	0.37	0.39

B, before pre-treatment; A, after clemastine

TABLE LXXXVI Effect of exercise on FVC following cimetidine in asthmatic patients (N = 10)

Patient No	Baseline FVC (l)		Absolute values for FVC after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
1	4.99	4.85	4.85	4.32	4.59	4.62	4.82
2	7.77	7.65	7.45	7.50	7.45	7.39	7.51
3	3.28	3.18	2.95	2.64	2.81	3.08	3.01
4	3.51	3.41	3.25	3.05	2.91	2.88	3.05
5	3.51	3.65	3.25	3.13	3.75	3.72	3.82
6	4.75	4.34	4.22	4.12	4.62	4.42	4.45
7	3.88	3.82	3.92	3.25	3.65	3.72	3.88
8	4.42	3.83	3.97	3.77	4.22	3.93	4.42
9	3.65	3.55	3.25	3.01	3.36	3.38	3.62
10	2.81	2.64	2.04	1.91	2.11	2.01	2.06
Mean	4.26	4.09	3.91	3.67	3.95	3.91	4.06
SEM	0.44	0.44	0.46	0.48	0.46	0.45	0.46

B, before pre-treatment; A, after cimetidine

TABLE LXXXVII Effect of exercise on MMEF following saline in asthmatic patients (N = 10)

Patient No	Baseline MMEF ($lsec^{-1}$) B	A	Absolute values for MMEF after exercise 2 min	5 min	10 min	15 min	20 min
1	3.42	3.39	2.64	1.45	1.53	1.79	1.96
2	4.45	4.63	3.65	3.23	2.78	3.15	3.87
3	2.00	2.22	0.98	0.75	0.81	0.85	0.71
4	1.99	2.01	1.80	0.92	0.83	0.74	0.70
5	2.83	2.97	1.13	1.02	1.17	1.51	1.43
6	2.97	3.01	2.41	1.76	1.88	1.99	2.12
7	2.35	3.57	1.96	1.50	1.99	1.97	2.13
8	1.79	1.79	1.25	1.19	1.15	1.12	1.26
9	2.63	2.53	2.22	1.36	1.63	2.05	1.79
10	1.08	0.87	0.65	0.57	0.65	0.54	0.57
Mean	2.55	2.70	1.87	1.37	1.44	1.57	1.65
SEM	0.30	0.33	0.29	0.24	0.21	0.25	0.31

B, before pre-treatment; A, after saline

TABLE LXXXVIII Effect of exercise on MMEF following clemastine in asthmatic patients (N = 10)

Patient No	Baseline MMEF (1 sec-1)		Absolute values for MMEF after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
1	2.89	3.40	2.30	1.61	1.26	1.20	17.3
2	4.53	4.71	4.15	3.87	2.98	3.66	4.13
3	1.51	2.34	1.97	1.23	1.28	1.50	1.68
4	2.36	3.47	3.41	3.11	2.38	3.07	3.07
5	3.12	3.04	2.49	2.05	2.26	2.31	2.45
6	3.25	2.60	1.95	1.77	2.06	2.33	2.21
7	3.12	3.16	5.02	1.90	2.68	2.70	2.85
8	1.87	2.16	1.99	1.46	1.61	1.38	1.46
9	2.98	2.90	2.39	0.91	1.82	1.95	1.87
10	1.93	1.89	1.28	0.90	0.80	0.82	0.82
Mean	2.76	2.97	2.69	1.88	1.91	2.09	2.22
SEM	0.28	0.25	0.36	0.30	0.22	0.28	0.30

B, before pre-treatment; A, after clemastine

TABLE LXXXIX Effect of exercise on MMEF following cimetidine in asthmatic patients (N = 10)

Patient No	Baseline MMEF (1 sec^{-1})		Absolute values for MMEF after exercise				
	B	A	2 min	5 min	10 min	15 min	20 min
1	3.56	3.47	3.23	2.30	2.57	2.53	2.90
2	4.61	4.65	4.42	3.83	3.37	3.79	4.32
3	1.62	1.95	1.28	1.13	1.27	1.26	1.51
4	2.84	2.53	1.87	1.47	1.48	1.40	1.52
5	1.95	2.70	1.39	1.27	1.70	1.72	1.77
6	2.62	3.08	2.33	1.92	2.10	2.49	2.60
7	2.12	2.46	2.31	1.54	1.80	1.71	1.44
8	1.77	1.56	1.65	1.25	1.41	1.34	1.64
9	2.00	1.46	1.77	1.06	1.21	1.26	1.40
10	1.28	0.88	0.62	0.61	0.63	0.53	0.73
Mean	2.44	2.47	2.09	1.64	1.75	1.80	1.98
SEM	0.32	0.35	0.34	0.28	0.24	0.29	0.32

B, before pre-treatment; A, after cimetidine

REFERENCES

REFERENCES

Adams, F. (1866) The extant works of Aretaeus, The Cappadocian. pp 316-318. London : The Sydenham Society.

Ahlquist, R.P. (1948) Study of adrenotropic receptors. American Journal of Physiology, 135, 586-600.

Alanko, K. & Poppius, H. (1973) Anticholinergic blocking of prostaglandin-induced bronchoconstriction. British Medical Journal, i, 294.

Allen, T.W., Addington, W., Rosendal, T. & Cugell, D.W. (1973) Alveolar carbon dioxide and airway resistance in patients with post-exercise bronchospasm. American Review of Respiratory Disease, 107, 816-821

Alps, B.J., Hill, M., Johnston, E.S. & Wilson, A.B. (1972) Quantitative analysis on isolated organs of the autonomic blocking properties of indoramin hydrochloride (Wy 21901). British Journal of Pharmacology, 44, 52-62.

Alston, W.C., Patel, K.R. & Kerr, J.W. (1974) Response of leucocyte adenyl cyclase to isoprenaline and effect of α blocking drugs in extrinsic bronchial asthma. British Medical Journal, i, 90-93.

Altounyan, R.E.C. (1964) Variation of drug action on airway obstruction in man. Thorax, 19, 406-415.

Altounyan, R.E.C. (1970) Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease. In Disodium Cromoglycate in Allergic Airways Disease, ed Pepys, J. & Frankland, A.W. pp 47-53. London : Butterworth.

Anderson, S.D., Seale, J.P., Rozea, P., Bandler, L., Theobald, G. & Lindsay, D.A. (1976) Inhaled and oral salbutamol in exercise-induced asthma. American Review of Respiratory Disease, 114, 493-500.

Anthracite, R.F., Vachon, L. & Knapp, P.H. (1971) Alpha-adrenergic receptors in the human lung. Psychosomatic Medicine, 33, 481-488.

Antic, R. & Macklem, P.T. (1976) The influence of clinical factors on site of airway obstruction in asthma. American Review of Respiratory Disease, 114, 851-859.

Arkins, J.A., Schleuter, D.P. & Fink, J.N. (1968) The effect of corticosteroids on methacholine inhalation in symptomatic bronchial asthma. Journal of Allergy, 41, 209-216.

Ash, A.S.F. & Schild, H.O. (1966) Receptors mediating some actions of histamine. British Journal of Pharmacology, 27, 427-439.

Assem, E.S.K. (1976) Current aspects in the immunopharmacology of asthma. Medical Biology, 54, 369-382.

Augstein, J., Cairns, H., Hunter, D., Lee, T.B., Suschitzky, J., Altounyan, R.E.C., Jackson, D.M., Mann, J., Orr, T.S.C. & Sheard, P. (1977) New orally effective chromone derivatives for the treatment of asthma. Agents and Actions, 7, 443-445.

Austen, K.F. (1971) Histamine and other mediators of allergic reactions. In Immunological Diseases, ed. Samter, M. pp 216-217. Boston: Little, Brown.

Austen, K.F. & Orange, R.P. (1975) Bronchial asthma: The possible role of the chemical mediators of immediate hypersensitivity in the pathogenesis of subacute chronic disease. American Review of Respiratory Disease, 112, 423-436.

Bedell, G.N., Marshall, R., DuBois, A.B. & Harris, J.H. (1956) Measurement of the volume of gas in the gastrointestinal tract. Values in normal subjects and ambulatory patients. Journal of Clinical Investigation, 35, 336-345.

Benson, M.K. (1975) Bronchial hyperreactivity. British Journal of Diseases of Chest, 69, 227-239.

Benson, M.K. & Graf, P.D. (1977) Bronchial reactivity: Interaction between vagal stimulation and inhaled histamine. Journal of Applied Physiology, 43, 643-647.

Bhat, K.N., Arroyave, C.M., Marney, S.R., Stevenson, D.D. & Tan, E.M. (1976) Plasma histamine changes during provoked bronchospasm in asthmatic patients. Journal of Allergy and Clinical Immunology, 58, 647-656.

Bianco, S., Griffin, J.P., Kamburoff, P.L. & Prime, F.J. (1972) The effect of thymoxamine on histamine induced bronchospasm in man. British Journal of Diseases of Chest, 66, 27-32.

Bianco, S., Griffin, J.P., Kamburoff, P.L. & Prime, F.J. (1974) Prevention of exercise-induced asthma by indoramin. British Medical Journal, iv, 18-20.

Bickerman, H.A. & Barach, A.L. (1954) The experimental production of cough in human subjects induced by citric acid aerosols. Preliminary studies on the evaluation of antitussive agents. American Journal of the Medical Sciences, 228, 156-163.

Birmingham, A.T. & Szolcsányi, J. (1965) Competitive blockade of adrenergic α-receptors and histamine receptors by thymoxamine. Journal of Pharmacy and Pharmacology, 17, 449-458.

Black, J.W., Duncan, W.A.M., Durant, C.J., Ganellin, C.R. & Parsons, M.E. (1972) Definition and antagonism of histamine H_2-receptors. Nature (London), 236, 385-390.

Black, J.W., Owen, D.A.A. & Parsons, M.E. (1975) An analysis of the depressor responses to histamine in the cat and dog: involvement of H_1- and H_2-receptors. British Journal of Pharmacology, 54, 319-324.

Blaschko, H. (1957) Formation of catecholamines in the animal body. British Medical Bulletin, 13, 162-165.

Boatman, E.S., Sato, S. & Frank, R. (1974) Acute effects of ozone on cat lungs. American Review of Respiratory Disease, 110, 157-169.

Borut, T.C., Tashkin, D.P., Fischer, T.J., Katz, R., Rachelefsky, G., Siegel, S.C., Lee, E. & Harper, C. (1977) Comparison of aerosolized atropine sulphate and SCH 1000 on exercise-induced bronchospasm in children. Journal of Allergy and Clinical Immunology, 60, 127-133.

Breslin, A.B.X. & Pepys, J. (1975) Effect of sodium cromoglycate on asthmatic reactions to environmental temperature changes. Clinical allergy, 5, 325-329.

Brinkman, G.L. (1968) The mast cell in normal human bronchus and lung. Journal of Ultrastructure Research, 23, 115-123.

Brocklehurst, W.E. (1962) Slow reacting substance and related compounds. In Progress in Allergy, ed. Kallos, P. & Waksman, B.H. pp 539-558. Basel: Skarger.

Brown, N.E., McFadden, E.R. & Ingram, R.H. (1977) Airway responses to inhaled histamine in asymptomatic smokers and nonsmokers. Journal of Applied Physiology, 42, 508-513.

Bryant, D.H. & Burns, M.W. (1976[a]) The relationship between bronchial histamine reactivity and atopic status. Clinical Allergy, 6, 373-381.

Bryant, D.H. & Burns, M.W. (1976[b]) Bronchial histamine reactivity: its relationship to the reactivity of the bronchi to allergens. Clinical Allergy, 6, 523-532.

Busse, W.W. & Sosman, J. (1977) Decreased H_2 histamine response of granulocytes of asthmatic patients. Journal of Clinical Investigation, 59, 1080-1087.

Cabezas, G.A., Graf, P.D. & Nadel, J.A. (1971) Sympathetic versus parasympathetic nervous regulation of airways in dogs. Journal of Applied Physiology, 31, 651-655.

Cade, J.F. & Pain, M.C.F. (1971) Role of bronchial reactivity in aetiology of asthma. Lancet, ii, 186-188.

Casterline, C.L., Evans, R. & Ward, G.W. (1976) The effect of atropine and albuterol aerosols on the human bronchial response to histamine. Journal of Allergy and Clinical Immunology, 58, 607-613.

Casterline, C.L. & Evans, R. (1977) Further studies on the mechanism of human histamine-induced asthma. Journal of Allergy and Clinical Immunology, 59, 420-424.

Castro de la Mata, R., Penna, M. & Aviado, D.M. (1962) Reversal of sympathomimetic bronchodilation by dichloroisoproterenol. Journal of Pharmacology and Experimental Therapeutics, 135, 197-203.

Cavanaugh, M.J. & Cooper, D.M. (1976) Inhaled atropine sulphate: dose response characteristics. American Review of Respiratory Disease, 114, 517-524.

Chand, N. & Eyre, P. (1975) Classification and biological distribution of histamine receptor subtypes. Agents and Actions, 5, 277-295.

Chan-Yeung, M. (1977) The effect of SCH 1000 and disodium cromoglycate on exercise-induced asthma. Chest, 71, 320-323.

Chan-Yeung, M., Vyas, M.N. & Grzybowski, S. (1971) Exercise-induced asthma. American Review of Respiratory Disease, 104, 915-923.

Chan-Yeung, M., Abboud, R., Tsao, M.S. & Maclean, L. (1976) Effect of helium on maximal expiratory flow in patients with asthma before and during induced bronchoconstriction. American Review of Respiratory Disease, 113, 433-443.

Chen, W.Y., Horton, D.J. & Souhrada, J.F. (1976) Respiratory tract and water loss and exercise-induced asthma. Physiologist, 19, 152.

Cherniack, R.M. & Raber, M.B. (1972) Normal standards for ventilatory function using an automated wedge spirometer. American Review of Respiratory Disease, 106, 38-46.

Ciba Foundation Study Group No.38 (1971) Identification of asthma, ed. Porter, R. & Birch, J. London: Churchill Livingstone.

Clarke, B.G., Guyatt, A.R., Alpers, J.H., Fletcher, C.M. & Hill, I.D. (1970) Changes in airways conductance on smoking a cigarette. Thorax, 25, 418-422.

Coca, A.F. & Cooke, R.A. (1923) On the classification of the phenomena of hypersensitiveness. Journal of Immunology, 8, 163-182.

Coca, A.F. & Grove, E. (1925) Studies in hypersensitiveness XIII A study of the atopic reagins. Journal of Immunology, 10, 445-464.

Cockcroft, D.W., Killian, D.N., Mellon, J.J.A. & Hargreave, F.E. (1977(a)). Bronchial reactivity to inhaled histamine: a method and clinical survey. Clinical Allergy, 7, 235-243.

Cockcroft, D.W., Killian, D.N., Mellon, J.J.A. & Hargreave, F.E. (1977(b)) Protective effect of drugs on histamine-induced asthma. Thorax, 32, 429-437.

Cockcroft, D.W., Ruffin, R.E. & Hargreave, F.E. (1978) Effect of SCH 1000 in allergen-induced asthma. Clinical Allergy, 8, 361-372.

Coleridge, H.M. & Coleridge, J.C.G. (1977) Impulse activity in afferent vagal C-fibres with endings in the intrapulmonary airways of dogs. Respiration Plysiology, 29, 125-142.

Conolly, M.E. & Greenacre, J.K. (1976) The lymphocyte β-adrenoceptor in normal subjects and patients with bronchial asthma. The effect of different forms of treatment on receptor function. Journal of Clinical Investigation, 58, 1307-1316.

Conolly, M.E. & Greenacre, J.K. (1977) The β-adrenoceptor of the human lymphocyte and human lung parenchyma. British Journal of Pharmacology, 59, 17-23.

Cooke, R.A. & Vander Veer, A. (1916) Human sensitization. Journal of Immunology, 1, 201-305.

Cookson, D.U. & Reed, C.E. (1963) A comparison of the effects of isoproterenol in normal and asthmatic subjects. American Review of Respiratory Disease, 88 636-643.

Costello, J.F., Sudlow, M.F., Douglas, N.J. & Flenley, D.C. (1975) Acute effects of smoking tobacco and tobacco substitute on lung function in man. Lancet, ii, 678-680.

Cotes, J.E. (1975) Lung Function. 3rd edition pp 386-387. Oxford: Blackwell.

Crompton, G.K. (1968) An unusual example of exercise-induced asthma. Thorax, 23, 164-167.

Cross, B.A., Guz, A., Jain, S.K., Archer, S., Stevens, J. & Reynolds, F. (1976) The effect of anaesthesia of the airway in dog and man: a study of respiratory reflexes, sensations and lung mechanics. Clinical Science and Molecular Medicine, 50, 439-454.

Cullen, W. (1827) The Works of William Cullen, M.D. ed. Thomson, J. Vol 11 pp 417-455. Edinburgh: Blackwood.

Curry, J.J. (1946) The action of histamine on the respiratory tract in normal and asthmatic subjects. Journal of Clinical Investigation, 25, 785-791.

Curry, J.J. (1947) Comparative action of acetyl-Beta-methycholine and histamine on the respiratory tract in normals, patients with hay fever, and subjects with bronchial asthma. Journal of Clinical Investigation, 26, 430-438.

Dain, D.S., Boushey, H.A. & Gold, W.M. (1975) Inhibition of respiratory reflexes by local anaesthetic aerosols in dogs and rabbits. Journal of Applied Physiology, 38, 1045-1050.

Dale, H.H. & Laidlaw, P.P. (1910) The physiological action of β -imidazolylethylamine. Journal of Physiology (London), 41, 318-344.

Da Silva, A.M.T. & Hamosh, P. (1973) Effect of smoking a single cigarette on the "small airway". Journal of Applied Physiology, 34, 361-365.

Davies, D.S. (1975) Pharmacokinetics of inhaled substances. Postgraduate Medical Journal, 51, 69-75.

Davies, S.E. (1968) Effect of disodium cromoglycate on exercise-induced asthma. British Medical Journal, iii, 593-594.

Deal, E.C., McFadden, E.R., Ingram, R.H. & Jaeger, J.J. (1978) Effects of atropine on potentiation of exercise-induced bronchospasm by cold air. Journal of Applied Physiology, 45, 238-243.

Dekock, M.A., Nadel, J.A., Zwi, S., Colebatch, H.J.H. & Olsen, C.R. (1966) New methods for perfusing bronchial arteries: histamine bronchoconstriction and apnea. Journal of Applied Physiology, 21, 185-194.

Despas, P.J., Leroux, M. & Macklem, P.T. (1972) Site of airways obstruction in asthma as determined by respiratory maximal expiratory flow breathing air and a helium-oxygen mixture. Journal of Clinical Investigation, 51, 3235-3243.

Devries, K., Goei, J.T., Booy-Noord, H., & Orie, N.G.M. (1962) Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. International Archives of Allergy and Applied Immunology, 20, 93-101.

Dimitrov-Szokodi, D., Husvéti, A. & Balogh, G. (1957) Lung denervation in the therapy of intractable bronchial asthma. Journal of Thoracic Surgery, 33, 166-184.

Douglas, W.W. (1975) Histamine and antihistamines; 5-hydroxytrytitamine and antagonists. In The Pharmacological Basis of Therapeutics, ed. Goodman, L.S. & Gilman, A. pp 590-629. London: Bailliere Tindall.

Drazen, J.M., Venugopalan, C.S. & Soter, N.A. (1978) H_2 receptor mediated inhibition of immediate type hypersensitivity reactions in vivo. American Review of Respiratory Disease, 117, 479-484.

DuBois, A.B., Botelho, S.Y., Bedell, G.N., Marshall, R. & Comroe, J.H. ($1956^{(a)}$) A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. Journal of Clinical Investigation, 35, 322-326.

DuBois, A.B., Botelho, S.Y. & Comroe, J.H. ($1956^{(b)}$) A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and patients with respiratory disease. Journal of Clinical Investigation, 35, 327-335.

DuBois, A.B. & Dautrebande, L. (1958) Acute effects of breathing inert dust particles and of carbechol aerosol on the mechanical characteristics of the lungs in man. Changes in response after inhaling sympathomimetic aerosols. Journal of Clinical Investigation, 37, 1746-1755.

Dunlop, L.S. & Smith, A.P. (1977) The effect of histamine antagonists on antigen-induced contractions of sensitized human bronchus in vitro. British Journal of Pharmacology, 59, 475P.

Dunnill, M.S., Masarella, G.R. & Anderson, J.A. (1969) A comparison of the quantitative anatomy of the bronchus in normal subjects, in status asthmaticus, in chronic bronchitis, and in emphysema. Thorax, 24, 176-179.

Edmunds, A.T., Tooley, M. & Godfrey, S. (1978) The refractory period after exercise-induced asthma: Its duration and relation to the severity of exercise. American Review of Respiratory Disease, 117, 247-254.

Edmunds, H.L., Graf, P.D. & Nadel, J.A. (1971) Reinnervation of reimplanted canine lung. Journal of Applied Physiology, 31, 722-727.

Eggleston, P.A. & Guerrant, J.L. (1976) A standardized method of evaluating exercise-induced asthma. Journal of Allergy and Clinical Immunology, 58, 414-425.

Eiser, N.M., Guz, A. & Snashall, P.D. (1978[a]) H_1 and H_2 receptor antagonists on bronchial dose-response curves to histamine in normal subjects. Clinical Science and Molecular Medicine, 54, 10P.

Eiser, N.M., Guz, A., Mills, J. & Snashall, P.D. (1978[b]) The effect of H_1 and H_2 receptor antagonists on antigen bronchial challenge. Thorax, 33, 534.

El-Bermani, A. & Grant, M. (1975) Acetylcholinesterase-positive nerves of the rhesus monkey bronchial tree. Thorax, 30, 162-170.

Empey, D.M., Laitinen, L.A., Jacobs, L., Gold, W.M. & Nadel, J.A. (1976) Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. American Review of Respiratory Disease, 113, 131-139.

Everitt, B.J. & Cairncross, K.D. (1969) Adrenergic receptors in the guinea pig trachea. Journal of Pharmacy and Pharmacology, 21, 97-102.

Eyre, P. (1973) Histamine H_2 -receptors in the sheep bronchus and cat trachea: The action of burimamide. British Journal of Pharmacology, 48, 321-323.

Eyre, P. & Deline, T.R. (1971) Release of dopamine from bovine lung by specific antigen and by compound 48/80. British Journal of Pharmacology, 42, 423-427.

Falck, B., Nystedt, T., Rosengren, E. & Stenflo, J. (1964) Dopamine and mast cells in ruminants. Acta Pharmacologica Toxicologica, 21, 51-58.

Ferris, L., Anderson, S.D. & Temple, D.M. (1978) Histamine release in exercise-induced asthma. British Medical Journal, ii, 1697.

Fillenz, M. (1970) Innervation of pulmonary and bronchial blood vessels of the dog. Journal of Anatomy, 106, 449-461.

Fillenz, M. & Widdicombe, J.G. (1972) Receptors of the lungs and airways; In Handbook of Sensory Physiology, Enteroceptors, ed. Neil, E. pp 81-112. New York: Springer-Verlag.

Fish, J.E., Rosenthal, R.R., Batra, G., Menkes, H., Summer, W., Permutt, S. & Normal, P. (1976) Airway responses to methacholine in allergic and non-allergic subjects. American Review of Respiratory Disease, 113, 579-586.

Fish, J.E., Rosenthal, R.R., Summer, W.R., Menkes, H., Norman, P.S. & Permutt, S. (1977) The effect of atropine on acute antigen-mediated airway constriction in subjects with allergic asthma. American Review of Respiratory Disease, 115, 371-379.

Fisher, H.K., Holton, P., Buxton, R. & Nadel, J.A. (1970) Mechanism of exercise-induced bronchospasm. American Review of Respiratory Disease, 101, 885-896.

Fisher, H.K. & Hansen, T.A. (1976) Site of action of inhaled 6 per cent carbon dioxide in the lungs of asthmatic subjects before and after exercise. American Review of Respiratory Disease, 114, 861-870.

Fitch, K.D., Turner, K.J. & Morton, A.R. (1972) The relationship between IgE levels and exercise-induced asthma. Annals of Allergy, 30, 497-501.

Fleisch, J.H., Maling, A.M. & Brodie, B.B. (1970) Evidence for existence of alpha-adrenergic receptors in the mammalian trachea. Americal Journal of Physiology, 218, 596-599.

Fleisch, J.H., Kent, K.M. & Cooper, T. (1973) Drug receptors in smooth muscle. In Asthma, Physiology, Immunopharmacology and Treatment, ed. Austen, K.F. & Lichtenstein, L.M. pp 139-167. New York: Academic Press.

Floyer, J. (1717) A Treatise of the Asthma 2nd edition pp 2-3. London: Wilkin and Innys.

Folkow, B. (1956) Structural, myogenic, humoral and nervous factors controlling peripheral resistance. In Hypertensive Drugs ed. Harington, M. pp 163-176. London: Pergamon Press.

Gaddie, J., Legge, J.S., Petrie, G. & Palmer, K.N. (1972) The effect of an alpha-adrenergic receptor blocking drug on histamine sensitivity in bronchial asthma. British Journal of Diseases of Chest, 66, 141-146.

Gayrard, P., Orehek, J. & Charpin, J. (1975) The prevention of the bronchoconstrictor effect of deep inspiration or of cigarette smoking in asthmatic patients by SCH 1000. Postgraduate Medical Journal, 51, 102.

Gibson, G.J., Greenacre, J.K., König, P., Conolly, M.E. & Pride, N.B. (1978) Use of exercise challenge to investigate possible tolerance to Beta-adrenoceptor stimulation in asthma. British Journal of Diseases of Chest, 72, 199-206.

Godfrey, S., Silverman, M. & Anderson, S.D. (1973) Problems of interpreting exercise-induced asthma. Journal of Allergy and Clinical Immunology, 52, 199-209.

Godfrey, S. (1975) Exercise-induced asthma - clinical, physiological, and therapeutic implications. Journal of Allergy and Clinical Immunology, 56, 1-17.

Godfrey, S. & König, P. (1976) Inhibition of exercise-induced asthma by different pharmacological pathways. Thorax, 31, 137-143.

Gold, W.M. (1975) The role of the parasympathetic nervous system in airways disease. Postgraduate Medical Journal, 51, 53-62.

Gold W.M., Kessler, G.F. & Yu, D.Y.C. (1972) Role of vagus nerves in experimental asthma in allergic dogs. Journal of Applied Physiology, 33, 719-725.

Goldberg, L.I. (1972) Cardiovascular and renal actions of dopamine: Potential clinical applications. Pharmacological Review, 24, 1-29.

Golden, J.A., Nadel, J.A. & Boushey, H.A. (1978) Bronchial hyperirritability in healthy subjects after exposure to ozone. American Review of Respiratory Disease, 118, 287-294.

Greengard, P. (1976) Possible role of cyclic nucleotides and phosphorylated membrane proteins in postsynaptic actions of neurotransmitters. Nature (London), 260, 101-108.

Grieco, M.H. & Pierson, R.N. (1970) Cardiopulmonary effects of methacholine in asthmatic and normal subjects. Journal of Allergy and Clinical Immunology, 45, 195-207.

Grieco, M.H. & Pierson, R.N. (1971) Mechanism of bronchoconstriction due to Beta-adrenergic blockade. Journal of Allergy and Clinical Immunology, 48, 143-152.

Gross, G.N., Souhrada, J.F. & Farr, R.S. (1974) The long term treatment of an asthmatic patient using phentolamine. Chest, 66, 397-401.

Hahn, H.L., Wilson, A.G., Graf, P.D., Fischer, S.P. & Nadel, J.A. (1978) Interaction between serotonin and efferent vagus nerves in dog lungs. Journal of Applied Physiology, 44, 144-149.

Harnett, J. & Spector, S.L. (1976) Blocking effect of SCH 1000, isoproterenol, and the combination on methacholine and histamine inhalations. Journal of Allergy and Clinical Immunology, 57, 261.

Harries, M.G., O'Brien, I.M. & Burge, P.S. (1979) Histamine release in experimentally induced asthma and urticaria. In Proceedings of the Mast Cell Symposium. ed Pepys, J. & Edwards, A.M. Turnbridge Wells: Pitiman Medical - in the press.

Hartley, J.P.R., Charles, T.J. & Seaton, A. (1977) Betamethasone valerate inhalation and exercise-induced asthma in adults. British Journal of Diseases of Chest, 71, 253-258.

Harvey, J.E. & Tattersfield, A.E. (1978) β-adrenergic responsiveness in asthma. Clinical Science and Molecular Medicine, 54, 24P-25P.

Haynes, R.L., Ingram, R.H. & McFadden, E.R. (1976) An assessment of the pulmonary response to exercise in asthma and an analysis of the factors influencing it. American Review of Respiratory Disease, 114, 739-752.

Henderson, W.R., Shelhamer, J.H., Reingold, D.B., Smith, L.J., Evans, R. & Kaliner, M. (1979) Alpha-adrenergic hyper-responsiveness in asthma. New England Journal of Medicine, 300, 642-647.

Hensley, M.J., O'Cain, C.F., McFadden, E.R. & Ingram, R.H. (1978) Distribution of bronchodilation in normal subjects: beta agonists versus atropine. Journal of Applied Physiology, 45, 778-782.

Hers, J.F.P. & Mulder, J. (1961) Broad aspects of the pathology and pathogenesis of human influenza. American Review of Respiratory Disease, 83, 84-97.

Herxheimer, H. (1946) Hyperventilation asthma. Lancet, i, 83-87.

Herxheimer, H. & Stresemann, E. (1961) The effect of bradykinin aerosol in guinea pigs and in man. Journal of Physiology (London), 158, 38P.

Herxheimer, H. & Stresemann, E. (1963) The effect of slow reacting substance (SRS-A) in guinea pigs and asthmatic patients. Journal of Physiology (London), 165, 78P-79P.

Hetzel, M.R., Batten, J.C. & Clark, T.J.H. (1977) Do sympathomimetic amines prevent exercise-induced asthma by bronchodilation alone? British Journal of Diseases of Chest, 71, 109-114.

Hirschowitz, B.I. (1979) H_2 histamine receptors. Annual Review of Pharmacology and Toxicology, 19, 203-244.

Hodgson, S.V., McPherson, A. & Friedman, M. (1974) The effect of betamethasone valerate aerosol on exercise-induced asthma in children. Postgraduate Medical Journal, 50 Supp 4, 69-73.

Holgate, S.T., Baldwin, C.J. & Tattersfield, A.E. (1977) β-adrenergic agonist resistance in normal human airways. Lancet, ii, 375-377.

Houssain, S. (1973) Quantitative measurement of bronchial muscle in man with asthma. American Review of Respiratory Disease, 107, 99-109.

Ingram, R.H., Wellmann, J.J., McFadden, E.R. & Mead, J. (1977) Relative contributions of large and small airways to flow limitation in normal subjects before and after atropine and isoprenaline. Journal of Clinical Investigation, 59, 696-703.

Ishizaka, K. (1975) Function of IgE antibody and regulation of IgE antibody response. In New Directions in Asthma, ed. Stein M. pp 133-148. Illinois: Park Ridge.

Ishizaka, K., Ishizaka, T. & Hornbrook, M.M. (1966) Physico-chemical properties of human reaginic antibody IV Presence of a unique immunoglobulin as a carrier of reaginic antibody. Journal of Immunology, 97, 75-85.

Ishizaka, K., Ishizaka, T. & Menzel, A.E.O. (1967) Physico-chemical properties of reaginic antibody VI Effect of heat on γE, γG and γA antibodies in the sera of ragweed-sensitive patients. Journal of Immunology, 99, 610-618.

Ishizaka, T., Ishizaka, K., Orange, R.P. & Austen, K.P. (1971) Pharmacologic inhibition of the antigen-induced release of histamine and slow reacting substance of anaphylaxis (SRS-A) from monkey lung tissues modulated by human IgE. Journal of Immunology, 106, 1267-1273.

Ishizaka, T., Soto, C.S. & Ishizaka, K. (1973) Mechanism of passive sensitisation. III Number of IgE molecules and their receptor sites on human basophil granulocytes. Journal of Immunology, 111, 500-511.

Itkin, I.H. & Anand, S.C. (1970) The role of atropine as a mediator blocker of induced bronchial obstruction. Journal of Allergy, 45, 178-186.

Jackson, D.M. & Richards, I.M. (1977) The effect of sodium cromoglycate on histamine aerosol-induced reflex bronchoconstriction in the anaesthetized dog. British Journal of Pharmacology, 61, 257-262.

Jain, S.K., Trenchard, D., Reynolds, E., Noble M.M. & Guz, A. (1973) The effect of local anaesthesia of the airway on respiratory reflexes in the rabbit. Clinical Science, 44, 519-538.

Johansson, S.G.O. (1967) Raised levels of a new immunoglobulin class (lgND) in asthma. Lancet, ii, 951-953.

Jones, R.S., Buston, M.H. & Wharton, M.J. (1962) The effect of exercise on ventilatory function in the child with asthma. British Journal of Diseases of Chest, 56, 78-86.

Jones, R.S., Wharton, M.J. & Buston, M.H. (1963) The place of physical exercise and bronchodilator drugs in the assessment of the asthmatic child. Archives of Disease of Childhood, 38, 539-545.

Kaliner, M., Orange, R.P. & Austen, K.F. (1972) Immunological release of histamine and slow reacting substance of anaphylaxis from human lung. IV Enhancement by cholinergic and alpha-adrenergic stimulation. Journal of Experimental Medicine, 136 556-567.

Kallós, P. (1971) Laboratory and clinical investigations of the antihistamine clemastine (Tavegyl). Clinical Trials Journal, 8, 23-26.

Kang, B., Townley, R.G., Lee, C.K. & Kolotkin, B.M. (1976) Bronchial reactivity to histamine before and after sodium cromoglycate in bronchial asthma. British Medical Journal, i, 867-870.

Katz, R.M., Whipp, B.J., Heimlich, E.M. & Wasserman, K. (1971) Exercise-induced bronchospasm, ventilation, and blood gases in asthmatic children. Journal of Allergy, 47, 148-158.

Key, B.M., Cain, S.M. & Goetter, W.E. (1978) Bronchoactive property of dopamine in the histamine infused dog. American Review of Respiratory Disease, 117, 136.

Kneussl, M.P. & Richardson, J.B. (1978) Alpha-adrenergic receptors in human and canine tracheal and bronchial smooth muscle. Journal of Applied Physiology, 45, 307-311.

Knowlton, G.C. & Larrabee, M.G. (1946) A unitary analysis of pulmonary volume receptors. American Journal of Physiology, 147, 100-114.

König, P., Jaffe, P. & Godfrey, S. (1974) The effect of corticosteroids on exercise-induced asthma. Journal of Allergy and Clinical Immunology, 54, 14-19.

Laitinen, L.A., Elkin, R.B., Empey, D.W., Jacobs, L., Mills, J., Gold, W.M. & Nadel, J.A. (1976) Changes in bronchial reactivity after administration of live attenuated influenza virus. American Review of Respiratory Disease, 113, 194.

Lee, T.P., Busse, W.W. & Reed, C.E. (1977) Effect of beta-adrenergic agonists, prostaglandins and cortisol on lymphocyte levels of cyclic adenosine monophosphate and glycogen. Abnormal lymphocyte metabolism in asthma. Journal of Allergy and Clinical Immunology, 59, 408-413.

Lefkowitz, R.J. (1975) Heterogeneity of adenylate cyclase-coupled β -adrenergic receptors. Biochemical Pharmacology, 24, 583-590.

Lichtenstein, L.M. (1973) The control of IgE-mediated histamine release: implications for the study of asthma. In Asthma Physiology, Immunopharmacology and Treatment, ed. Austen, K.F. & Lichtenstein, L.M. pp 91-107. New York: Academic Press.

Little, J.W., Hall, W.J., Douglas, R.G., Mudholkar, G.S., Speers, D.M. & Patel, K. (1978) Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. American Review of Respiratory Disease, 118, 295-303.

Logsdon, P.A., Middleton, E. & Coffey, R.G. (1972) Stimulation of leukocyte adenyl cyclase by hydrocortisone and isoproterenol in asthmatic and non-asthmatic subjects. Journal of Allergy and Clinical Immunology, 50, 45-56.

Loring, S.H., Drazen, J.M. & Ingram, R.H. (1977) Canine pulmonary response to aerosol histamine: direct versus vagal effects. Journal of Applied Physiology, 42, 946-952.

Loring, S.H., Drazen, J.M., Snapper, J.R. & Ingram, R.H. (1978) Vagal and aerosol histamine interactions on airway responses in dogs. Journal of Applied Physiology, 45, 40-44.

Major, R.H. (1948) In Classic Descriptions of Disease, 3rd edition, pp 577-580. London: Blackwell.

Makino, S. (1966) Clinical significance of bronchial sensitivity to acetylcholine and histamine in bronchial asthma. Journal of Allergy, 38, 127-142.

Makino, S., Ikemori, K., Kashima, T. & Fukuda, T. (1977) Comparison of cyclic adenosine monophosphate response of lymphocytes in normal and asthmatic subjects to norepinephrine and salbutamol. Journal of Allergy and Clinical Immunology, 59, 348-352.

Mathé, A.A., Hedquist, P., Holmgren, A. & Suanborg, N. (1973) Bronchial hyperreactivity to prostaglandin F2 α and histamine in patients with asthma. British Medical Journal, i, 193-196.

Mathé, A.A. & Hedquist, P. (1975) Effect of prostaglandins F2 α and E2 on airway conductance in healthy subjects and asthmatic patients. American Review of Respiratory Disease, 111, 313-320.

Maudsley, D.V., Kobayashi, Y., Williamson, E. & Bovaird, L. (1973) H_2-receptor blockade and stimulation of histidine decarboxylase. Nature (New Biology), 245, 148-149.

Mead, J., Turner, M.J., Macklem, P.T. & Little, J.B. (1967) Significance of the relationship between lung recoil and maximum expiratory flow. Journal of Applied Physiology, 22, 95-108.

Mellis, C.M., Kattan, M., Keens, T. & Levison, H. (1978) Comparative study of histamine and exercise in asthmatic children. American Review of Respiratory Disease, 117, 911-915.

Meltzer, S.J. (1910) Bronchial asthma as a phenomenon of anaphylaxis. Journal of the American Medical Association, 55, 1021-1024.

Middleton, E. & Finke, S.R. (1968) Metabolic response to epinephrine in bronchial asthma. Journal of Allergy, 42, 288-299.

Mills, J.E., Sellick, H. & Widdicombe, J.G. (1969) Activity of lung irritant receptors in pulmonary microembolism, anaphylaxis, and drug-induced bronchoconstrictions. Journal of Physiology (London), 203, 337-357.

Mills, J.E. & Widdicombe, J.G. (1970) Role of the vagus nerves in anaphylaxis and histamine-induced bronchoconstriction in guinea-pigs. British Journal of Pharmacology, 39, 724-731.

Morris, H.G., Rusnak, S.A., Selner, J.C., Barzens, K., Barnes, J. (1978) Comparative effects of ephedrine on adrenergic responsiveness in normal and asthmatic subjects. Journal of Allergy and Clinical Immunology, 61, 294-302.

Morton, A.R., Turner, K.J. & Fitch, K.D. (1973) Protection from exercise-induced asthma by pre-exercise cromolyn sodium and its relationship to serum IgE levels. Annals of Allergy, 31, 265-271.

Muranaka, M., Suzuki, S., Miyamoto, T., Takeda, K., Okumura, H. & Makino, S. (1974) Bronchial reactivities to acetycholine and IgE levels in asthmatic subjects after long-term remissions. Journal of Allergy and Clinical Immunology, 54, 32-40.

MacDonald, A.G., Ingram, C.G. & McNeill, R.S. (1967) The effect of propranolol on airway resistance. British Journal of Anaesthesia, 39, 919-926.

McDonald, R.H., Goldberg, L.I., McNay, J.L. & Tuttle, E.P. (1964) Effect of dopamine in man: augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. Journal of Clinical Investigation, 43, 1116-1124.

McFadden, E.R., Newton-Howes, J. & Pride, N.B. (1970) Acute effects of inhaled isoproterenol on the mechanical characteristics of the lungs in normal man. Journal of Clinical Investigation, 49, 779-790.

McFadden, E.R. & Linden, D.A. (1972) A reduction in maximum mid-expiratory flow rate; a spirographic manifestation of small airway disease. American Journal of Medicine, 52, 725-737.

McFadden, E.R., Stearns, D.R., Ingram, R.H. & Leith, D.E. (1977[a]) Relative contribution of hypocarbia and hyperpnea as mechanisms in post-exercise asthma. Journal of Applied Physiology, 42, 22-27.

McFadden, E.R., Ingram, R.H., Haynes, R.L. & Wellman, J.J. (1977[b]) Predominant site of flow limitation and mechanisms of post-exertional asthma. Journal of Applied Physiology, 42, 746-752.

McFadden, E.R. & Ingram, R.H. (1979) Exercise-induced asthma. New England Journal of Medicine, 301, 763-769.

McNally, J.F., Enright, P. & Souhrada, J.F. (1978) The role of the oropharynx in exercise-induced asthma. American Review of Respiratory Disease, 117, 372A.

McNay, J.L. & Goldberg, L.I. (1966) Comparison of the effects of dopamine, isoproterol, norepinephrine and bradykinin on canine renal and femoral blood flow. Journal of Pharmacology and Experimental Therapeutics, 151, 23-31.

McNeill, R.S. (1964) Effect of beta-adrenergic blocking agent, propranolol, on asthmatics. Lancet, ii, 1101-1102.

McNeill, R.S., Nairn, J.R., Millar, J.S. & Ingram, C.G. (1966) Exercise-induced asthma. Quarterly Journal of Medicine, 35, 55-67.

Nadel, J.A. (1973) Neurophysiologic aspects of asthma. In Asthma, Physiology, Immunopharmacology and Treatment, ed. Austen, K.F. & Lichtenstein, L.M. pp 29-38. New York: Academic Press.

Nadel, J.A. (1977) Autonomic control of airway smooth muscle and airway secretions. American Review of Respiratory Disease, 115 Suppl, 117-126.

Nadel, J.A. & Comroe, J.H. (1961) Acute effects of inhalation of cigarette smoke on airway conductance. Journal of Applied Physiology, 16, 713-716.

Nakazawa, T., Toyoda, T., Furukawa, M. Taya, T. & Kobayashi, S. (1976) Inhibitory effects of various drugs on dual asthmatic responses in wheat flour-sensitive subjects. Journal of Allergy and Clinical Immunology, 58, 1-9.

Newball, H.H. & Lenfant, C. (1977) The influence of atropine and cromolyn on human bronchial hyperreactivity to aerosolized prostaglandin F_2 α Respiration Physiology, 30, 125-136.

Newman Taylor, A.J., Soutar, C., Sneerson, J. & Turner-Warwick, M. (1976) Bromocriptine in the treatment of intractable asthma. Thorax, 31, 488.

Nikerson, M. & Collier, B. (1975) Drugs inhibiting adrenergic nerves and structures innervated by them. In The Pharmacological Basis of Therapeutics. 5th edition, ed. Goodman, L.S. & Gilman, A. pp 533-564. London: Bailliere Tindall.

Nogrady, S.G., Hartley, J.P.R., Hanslip, P.D.J. & Hurst, N.P. (1978) Bronchodilation after inhalation of the antihistamine clemastine. Thorax, 33, 479-482.

Nogrady, S.G. & Bevan, C. (1978) Inhaled antihistamines - bronchodilation and effects on histamine - and methacholine - induced bronchoconstriction. Thorax, 33, 700-704.

Olsen, C.R., Colebatch, H.J.H., Mebel, P.E., Nadel, J.A. & Staub, N.C. (1965) Motor control of pulmonary airways studied by nerve stimulation. Journal of Applied Physiology, 20, 202-208.

Orange, R.P. (1973) Immunopharmacological aspects of bronchial asthma. Clinical Allergy, 3, 521-537.

Orange, R.P., Valentine, M.D. & Austen, K.F. (1968) Inhibition of the release of slow-reacting substance of anaphylaxis in the rat with diethylcarbamazine. Proceedings of the Society Experimental Biology and Medicine, 127, 127-132.

Orehek, J., Gayrard, P., Grimaud, C. & Charpin, J. (1975(a)) Effect of beta-adrenergic blockade on bronchial sensitivity to inhaled acetycholine in normal subjects. Journal of Allergy and Clinical Immunology, 55, 164-169.

Orehek, J., Gayrard, P., Grimaud, C. & Charpin, J. (1975(b)) Effect of maximal respiratory manoeuvres on bronchial sensitivity of asthmatic patients as compared to normal people. British Medical Journal, i, 123-125.

Orehek, J., Gayrard, P., Smith, A.P., Grimaud, C. & Charpin, J. (1977(a)) Airway response to carbachol in normal and asthmatic subjects. American Review of Respiratory Disease, 115, 937-943.

Orehek, J., Gayrard, P., Grimaud, C. & Charpin, J. (1977(b)) Bronchial response to inhaled prostaglandin $F_{2\alpha}$ in patients with common or aspirin-sensitive asthma. Journal of Allergy and Clinical Immunology, 59, 414-419.

Orehek, J. & Gayrard, P. (1977) Atropine effect on antigen-mediated airway constriction. American Review of Respiratory Disease, 115, 792-793.

Orr, T.S.C., Pollard, M.C., Gwilliam, J. & Cox, J.S.G. (1970) Mode of action of disodium cromoglycate, studies on immediate type hypersensitivity reactions using "Double Sensitization" with two antigenically distinct reagins. Clinical Experimental Immunology, 7, 745-757.

Owen, D.A.A. (1977) Histamine receptors in the cardiovascular system. General Pharmacology, 8, 141-156.

Paintal, A.S. (1977) The nature and effects of sensory inputs into the respiratory centres. Federation Proceedings, 36, 2428-2432.

Parker, C.D., Bilbo, R.E. & Reed, C.E. (1965) Methacholine aerosol as test for bronchial asthma. Archives of Internal Medicine, 115, 452-458.

Parker, C.W. & Smith, J.W. (1973) Alterations in cyclic adenosine monophosphate metabolism in human bronchial asthma. I Leukocyte responsiveness to beta-adrenergic agents. Journal of Clinical Investigation, 52, 48-59.

Parish, W.E. (1970) Short term anaphylactic IgG antibodies in human sera. Lancet, ii, 591-592.

Parsons, M.E. (1977) The antagonism of histamine H_2 receptors in vitro and in vivo with particular reference to the actions of cimetidine. In Cimetidine, Proceedings of Second International Symposium on Histamine H_2-receptor antagonists, ed. Burland, W.L. & Simkins, M.A. pp 13-22. Amsterdam: Excerpta Medica.

Patel, K.R. (1975) Atropine, sodium cromoglycate and thymoxamine on $PGF_2\alpha$ -induced bronchoconstriction in extrinsic asthma. British Medical Journal, ii, 360-362.

Patel, K.R. & Kerr, J.W. (1973) The effect of alpha and beta receptor blockade on the control of airway calibre in bronchial asthma. Clinical Allergy, 3, 439-448.

Patel, K.R. & Kerr, J.W. (1975) Effect of alpha receptor blocking drug, thymoxamine, on allergen induced bronchoconstriction in extrinsic asthma. Clinical Allergy, 5, 311-316.

Patel, K.R., Kerr, J.W., MacDonald, E.B. & MacKenzie, A.M. (1976) The effect of thymoxamine and cromolyn sodium on post-exercise bronchoconstriction in asthma. Journal of Allergy and Clinical Immunology, 57, 285-292.

Patterson, R., Fink, J.N., Nishimura, E.T. & Pruzansky, J.J. (1965) The passive transfer of immediate type hypersensitivity from man to other primates. Journal of Clinical Investigation, 44, 140-148.

Patterson, R., Tomita, Y., Oh, S.H., Susizka, I.M. & Pruzansky, J.J. (1974) Respiratory mast cells and basophiloid cells. I Evidence that they are secreted into the bronchial lumen, morphology, degranulation, and histamine release. Clinical Experimental Immunology, 16, 223-234.

Patterson, R., McKenna, J.M., Suszka, I.M., Solliday, N.H., Pruzansky, J.J., Roberts, M. & Kehoe, T.J. (1977) Living histamine-containing cells from the bronchial lumens of humans. Description and comparison of histamine content with cells of rhesus monkeys. Journal of Clinical Investigation, 59, 217-225.

Patterson, R., Suszka, I.M. & Harris, K.E. (1978) In in vivo transfer of antigen-induced airway reactions by bronchial lumen cells. Journal of Clinical Investigation, 62, 519-524.

Pepys, J. (1975) In Clinical Aspects of Immunology, 3rd edition, ed. Gell, P.G.H., Coombs, R.A. & Lachman, P.J. pp 887-902. Oxford: Blackwell.

Petit, J.M. & Delhez, L. (1970) Quelques donées experimentales recéntes concernant l'origine de la dyspneé et la régulation ventilatoire chez le malade asthmatique. Acta Tuberculosa et Pneumologica Belgica, 61, 169-186.

Pollock, R., Gregory, N.L., Shaw, A. & Patel, K.R. (1977) Improved technique for recording respiratory data. Medical and Biological Engineering and Computing, 15, 541-547.

Popa, V.T. (1977) Bronchodilating activity of an H_1 blocker, chlorpheniramine. Journal of Allergy and Clinical Immunology, 59, 54-63.

Poppius, H., Salorinne, Y. & Vilzanen, A.A. (1972) Inhalation of a new anticholinergic drug, SCH 1000, in asthma and chronic bronchitis: Effect on airway resistance, thoracic gas volume, blood gases and exercise-induced asthma. Bulletin de Physio-Pathologie Respiratoire, 8, 643-652.

Powell, J.R. & Brody, J.M. (1976) Participation of H_1 and H_2 histamine receptors in physiological vasodilator responses. American Journal of Physiology, 231, 1002-1009.

Pride, N.B. (1971) The assessment of airflow obstruction. British Journal of Diseases of Chest, 65, 135-169.

Radermecker, M., Guebelle, F. & Salmon, J. (1972) Inhalation tests in monkeys passively sensitized with human serum. Clinical Allergy, 2, 247-259.

Reeves, W.G. (1977) Atopic disorders. In Immunology in Medicine. ed. Holborow, E.J. & Reeves, W.G. pp 763-771. London: Academic Press.

Richardson, J.B. & Bouchard, T. (1975) Demonstration of a nonadrenergic inhibitory nervous system in the trachea of the guinea-pig. Journal of Allergy and Clinical Immunology, 56, 473-480.

Richardson, J.B. & Beland, J. (1976) Nonadrenergic inhibitory nervous system in human airways. Journal of Applied Physiology, 41, 764-771.

Richardson, P.S. & Sterling, G.M. (1969) Effects of α -adrenergic receptor blockade on airway conductance and lung volumes in normal and asthmatic subjects. British Medical Journal, ii, 143-145.

Römer, D. & Weidman, H. (1966) Pharmacological studies on the new antihistamine Tavegil. Medizinische Welt, 17, 2791-2794.

Rosenthal, R.R., Norman, P.S., Summer, W.R. & Permutts, S. (1977) Role of the parasympathetic system in antigen-induced bronchospasm. Journal of Applied Physiology, 42, 600-606.

Rubinfield, A.R. & Pain, M.C.F. (1977) Relationship between bronchial reactivity, airway calibre and severity of asthma. American Review of Respiratory Disease, 115, 381-387.

Rudolf, M., Grant, B.J.B., Saunders, K.B., Brostoff, J., Salt, P.J. & Walker, D.I. (1975) Aspirin in exercise-induced asthma. Lancet, i, 450.

Ruffin, R.E., Cockcroft, D.W. & Hargreave, F.E. (1978) A comparison of the protection effect of fenoterol and SCH 1000 on allergen-induced asthma. Journal of Allergy and Clinical Immunology, 61, 42-47.

Salter, H.H. (1868) On asthma, its pathology and treatment. 2nd edition. pp 24-60. London.

Sampson, S.R. & Vidruk, E.H. (1975) Properties of irritant receptors in canine lung. Respiration Physiology, 25, 9-22.

Scadding, J.G. (1977) In Asthma. ed. Clark, T.J.H. & Godfrey, S. pp 1-10. London: Chapman & Hall.

Schachter, E.N. Kreisman, H., Littner, M., Beck, G.J. & Voncken, F. (1978) Airway responses to exercise in mild asthmatics. Journal of Allergy and Clinical Immunology, 61, 390-398.

Seale, J.P. & Piper, P.J. (1978) Chemical mediators and non-allergic asthma. Lancet, ii, 1265.

Seaton, A., Davies, G., Gaziana, D. & Hughes, R.O. (1969) Exercise-induced asthma. British Medical Journal, iii, 556-558.

Sellick,H. & Widdicombe, J.G. (1971) Stimulation of lung irritant receptors by cigarette smoke, carbon dust and histamine aerosol. Journal of Applied Physiology, 31, 15-19.

Shturman-Ellstein, R., Zeballos, R.J., Buckley, J.M. & Souhrada, J.F. (1978) The benefician effect of nasal breathing on exercise-induced bronchoconstriction. American Review of Respiratory Disease, 118, 65-73.

Siegal, S. (1956) Non-parametric Statistics for the Behavioural Sciences. pp 95-126. New York: McGraw-Hill.

Silverman, M., Anderson, S.D. & Walter, S.R. (1972) Metabolic changes preceding exercise-induced bronchoconstriction. British Medical Journal, i, 207-209.

Silverman, M. & Anderson, S.D. (1972) Standardization of exercise tests in asthmatic children. Archives of Diseases of Children, 47, 882-889.

Simon, R.A., Stevenson, D.D., Arroyave, C.M. & Tan, E.M. (1977) The relationship of plasma histamine to the activity of bronchial asthma. Journal of Allergy and Clinical Immunology, 60, 312-316.

Simonsson, B.G. (1972) Reflex control of airways calibre. Bulletin de Physio-Pathologie Respiratoire, 8, 439-446.

Simonsson, B.G., Jacobs, F.M. & Nadel, J.A. (1967) Role of autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airway disease. Journal of Clinical Investigation, 46, 1812-1818.

Simonsson, B.G., Svendmyr, N. Skoogh, B.-E., Anderson, R. & Bergh, N.P. (1972[a]) In vivo and in vitro studies on alpha-receptors in human airways. Potentiation with bacterial endotoxin. Scandinavian Journal of Respiratory Diseases, 53, 227-236.

Simonsson, B.G., Skoogh, B.E. & Ekström-Jodal, B. (1972[b]) Exercise-induced airways constriction. Thorax, 27, 169-180.

Simonsson, B.G., Skoogh, B.-E., Bergh, N.P., Anderson, R. & Svedmyr, H. (1973) In vivo and in vitro effect of bradykinin on bronchial motor tone in normal subjects and patients with airways obstruction. Respiration, 30, 378-388.

Sly, R.M., Heimlich, E.M., Busser, R.J. & Strick, L. (1967) Exercise-induced bronchospasm: effect of adrenergic and cholinergic blockade. Journal of Allergy, 40, 93-99.

Sly, R.M. & Matzen, K. (1974) Effect of diethylcarbamazine pamoate upon exercise-induced obstruction in asthmatic children. Annals of Allergy, 33, 138-144.

Smith, A.P. & Dunlop, L.S. (1975) Prostaglandins and asthma. Lancet, i, 39.

Smith, A.P., Cuthbert, M.F. & Dunlop, L.S. (1975) Effects of inhaled prostaglandins E_1 , E_2 and $F_{2\alpha}$ on the airway resistance of healthy and asthmatic man. Clinical Science and Molecular Medicine, 48 421-430.

Smith, D.E. (1963) Electron microscopy of normal mast cells under various experimental conditions. Annals of New York Academy of Sciences, 103, 40-52.

Snashall, P.D., Boother, F.A. & Sterling, G.M. (1978) The effect of α -adrenoreceptor stimulation on the airways of normal and asthmatic man. Clinical Science and Molecular Medicine, 54, 283-289.

Spectors, S.L. & Farr, R.S. (1975) A comparison of methacholine and histamine inhalations in asthmatics. Journal of Allergy and Clinical Immunology, 56, 308-316.

Spectors, S.L. & Farr, R.S. (1976) Atopy reconsidered. Clinical Allergy, 6, 83-90.

Stanworth, D.R., Humphrey, J.H., Bennich, H. & Johansson, S.G.O. (1968) Inhibition of Prausnitz-Küstner reaction by proteolytic-cleavage fragments of a human myeloma protein of immunoglobulin Class E. Lancet, ii, 17-18.

Stemmann, E.A. & Kosche, F. (1975) A comparison of the effects of SCH 1000 MDI, sodium cromoglycate, and beta-adrenergic drugs on exercise-induced asthma in children. Postgraduate Medical Journal, 51, 105.

Sterling, G.M. (1967) Mechanism of bronchoconstriction caused by cigarette smoking. British Medical Journal, iii, 275-277.

Stevenson, D.D., Arroyave, C.M., Bhat, K.N. & Tan, E.M. (1976) Oral ASA challenges in asthmatic patients: a study of plasma histamine. Clinical Allergy, 6, 493-505.

Stransky, A., Szereda-Przestaszewska, M. & Widdicombe, J.G. (1973) The effect of lung reflexes on laryngeal resistance and motoneurone discharge. Journal of Physiology (London), 231, 417-438.

Strauss, R.H., Haynes, R.L., Ingram, R.H. & McFadden, E.R. (1977[a]) Comparison of arm versus leg work in introduction of acute episodes of asthma. Journal of Applied Physiology, 42, 565-570.

Strauss, R.H., McFadden, E.R., Ingram, R.H. & Jaeger, J.J. (1977[b]) Enhancement of exercise-induced asthma by cold air. New England Journal of Medicine, 293, 743-747.

Strauss, R.H., Ingram, R.H. & McFadden, E.R. (1977[c]) A critical assessment of the roles of circulating hydrogen ion and lactate in the production of exercise-induced asthma. Journal of Clinical Investigation, 60, 658-664.

Strauss, R.H., McFadden, E.R., Ingram, R.H., Deal, E.C. & Jaeger, J.J. (1978) Influence of head and humidity on the airway obstruction induced by exercise in asthma. Journal of Clinical Investigation, 61, 433-440.

Szentivanyi, A. (1968) The Beta adrenergic theory of the atopic abnormality in bronchial asthma. Journal of Allergy, 42, 203-232.

Szereda-Przestaszewska, M. (1974) Changes in laryngeal calibre in anaphylactic shock in rabbits. Journal of Physiology (London), 241, 21P-22P.

Taylor, S.H., Sutherland, G.R., MacKenzie, G.J., Staunton, H.P. & Donald, K.W. (1965) The circulatory effects of phentolamine in man with particular respect to changes in forearm blood flow. Clinical Science 28, 265-284.

Thomas, L.L., Bochner, B.S. & Lichtenstein, L.M. (1978) Inhibition of human polymorphonuclear leukocyte-derived histaminase activity by H_2 antagonists. Biochemical Pharmacology, 27, 2562-2565.

Thorner, M.O. (1975) Dopamine is an important neurotransmitter in the autonomic nervous system. Lancet, i, 662-664.

Tinkelman, D.G., Cavenaugh, M.J. & Cooper, D.M. (1976) Inhibition of exercise-induced bronchospasm by atropine. American Review of Respiratory Disease, 114, 87-94.

Townley, R.G., Ryo, U.Y. & Kang, B. (1971) Bronchial sensitivity to methacholine in asthmatic subjects free of symptoms for one to twenty-one years. Journal of Allergy, 47, 91-92.

Townley, R.G., Guirgis, H.A., Kolotkin, B., Jirka, A., Vlagopoulos, T. & Nakazawa, H. (1974) Methacholine sensitivity and atopic disease in asthmatic and nonatopic families. Journal of Allergy and Clinical Immunology, 53, 107.

Ts'ao, C., Patterson, R., McKenna, J.M. & Suszka, I.M. (1977) Ultrastructural identification of mast cells obtained from human bronchial lumens. Journal of Allergy and Clinical Immunology, 59, 320-326.

Turner-Warwick, M. (1978) The asthmas. In Immunology of the Lung, Chap 3, pp 63. London: Edward Arnold.

Vane, J.R. (1971) Mediators of the anaphylactic reaction. In Identification of Asthma. Ciba Foundation Symposium Study Group No. 38. ed. Porter, R. & Birch, J. pp 121-131. London: Churchill Livingstone.

Vassallo, C.J., Gee, J.B.L. & Domm, B.M. (1972) Exercise-induced asthma. American Review of Respiratory Disease, 105, 42-49.

Vidruk, E.H., Hahn, H.L., Nadel, J.A. & Sampson, S.R. (1977) Mechanisms by which histamine stimulates rapidly adapting receptors in dog lungs. Journal of Applied Physiology, 43, 397-402.

Vincent, N.J., Knudson, R., Leith, D.E., Macklem, P.T. & Mead, J. (1970) Factors influencing pulmonary resistance. Journal of Applied Physiology, 20, 236-243.

Von Essen, C. (1972) Effects of dopamine, noradrenaline and 5-hydroxytryptamine on the cerebral blood flow in the dog. Journal of Pharmacy and Pharmacology, 24, 668.

Von Euler, U.S. & Lishajko, F. (1957) Dopamine in mammalian lung and spleen. Acta Physiologica Pharmacologica Neerlandica, 6, 295-303.

Wasserman, S.I., Soter, N.A., Canter, D.M. & Austen, K.F. (1977) Cold urticaria: recognition and characterization of a neutrophil chemotactic factor which appears in the serum during experimental cold challenge. Journal of Clinical Investigation, 60, 189-196.

Weidmann, H., Grauwiler, J., Griffith, R., Römer, D., Taeschler, M. & Zehnder, K. (1967) Farmacologia, Farmacounetica E Tossicologia del Nuovo Anti-staminico HS 592 (Tavegil) Estratto du Bottettino Chimico Farmaceutico, 106, 467-496.

Weiss, E.B., Hargraves, W.A. & Viswanath, S.G. (1978) The inhibitory action of lidocaine in anaphylaxis. American Review of Respiratory Disease, 117, 859-869.

Weiss, S., Robb, G.P. & Blumgart, H.C. (1929) The velocity of blood flow in health and disease as measured by the effect of histamine on the minute vessels. American Heart Journal, 4, 664-691.

Wells, R.E., Walker, J.E.C. & Hickler, R.B. (1960) Effects of cold air on respiratory air flow resistance in patients with respiratory tract disease. New England Journal of Medicine, 263, 268-273.

Whitsett, T.L. & Goldberg, L.I. (1972) Effects of levodopa on systolic pre-ejection period, blood pressure and heart rate during acute and chronic treatment of Parkinson's disease. Circulation, 45, 97-106.

Widdicombe, J.G. (1961) Respiratory reflexes in man and other mammalian species. Clinical Science, 21, 163-170.

Widdicombe, J.G. (1963) Regulation of tracheo-bronchial smooth muscle. Physiological Reviews, 43, 1-37.

Widdicombe, J.G. (1974) Reflex control of breathing. In Respiratory Physiology,MTP International Review of Science, ed. Widdicombe, J.G. Vol 2, pp 273-302. London: Butterworth.

Widdicombe, J.G. (1975) Reflex control of airways smooth muscle. Postgraduate Medical Journal, 51, 36-43.

Widdicombe, J.G. (1977) Some experimental models of acute asthma. Journal of the Royal College of Physicians, 11, 141-155.

Widdicombe, J.G., Kent, D.C. & Nadel, J.A. (1962) Mechanism of bronchoconstriction during inhalation of dust. Journal of Applied Physiology, 17, 613-616.

Widdicombe, J.G. & Stirling, G.M. (1970) The autonomic nervous system and breathing. Archives of Internal Medicine, 126, 311-328.

Wide, L., Bennich, H. & Johansson, S.G.O. (1967) Diagnosis of allergy by an in vitro test for allergen antibodies. Lancet, ii, 1105-1107.

Woenne, R., Kattan, M., Orange, R.P. & Levison, H. (1978) Bronchial hyperreactivity to histamine and methacholine in asthmatic children after inhalation of SCH 1000 and chlorpheniramine maleate. Journal of Allergy and Clinical Immunology, 62, 119-124.

Woolcock, A.J., Colman, M.H. & Jones, M.W. (1978) Atopy and bronchial reactivity in Australian and Melanesian populations. Clinical Allergy, 8, 155-164.

Yu, D.Y.C., Galant, S.P. & Gold, W.M. (1972) Inhibition of antigen-induced bronchoconstriction by atropine in asthmatic children. Journal of Applied Physiology, 32, 823-828.

Zaid, G. & Beall, G.N. (1966) Bronchial response to Beta adrenergic blockade. New England Journal of Medicine, 275, 580-584.

Zeballos, R.J., Shturman-Ellstein, R., McNally, J.F., Hirsch, J.E. & Souhrada, J.F. (1978) The role of hyperventilation in exercise-induced broncho-constriction. American Review of Respiratory Disease, 118, 877-884.