MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

August 19, 1976

Alan K. Pierce, M.D.

RECENT ADVANCES IN THE THERAPY OF ASTHMA

MECHANISMS OF ASTHMA

Mediator Release

Increased Parasympathetic Activity

Abnormality of the Adrenergic Nervous System

THERAPEUTIC AGENTS

Cromolyn

Theophylline

Selective β Agonists

Topical Inhaled Steroids

RECENT ADVANCES IN THE THERAPY OF ASTHMA

The most widely accepted definition of asthma is that of the American Thoracic Society (1). "Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy." Although useful clinically, the definition implies a unitary cause of this symptom complex. It is important to realize that such may not be the case. That is, not only may asthmatic attacks be precipitated by different triggers, but it may be that the underlying defect is not the same in all patients. Such was suggested years ago by the differentiation of patients into the categories of extrinsic and instrinsic asthma (2).

This concept has been refined by the clinical studies of the group at Scripps Clinic (3-6) who attempted to categorize the apparent mode of onset of asthma of 234 consecutive patients presenting to them. It was found that in only 50% of patients could some specific mechanism even be suggested as a cause of asthma. In the remainder of their patients, the findings were too complex or too ill-defined to allow categorization.

These clinical findings suggest that the three major theories of the mechanisms of asthma each may be correct for selected patients or that individual patients may have one or more of the postulated defects in varying combinations. However, in order to better understand the new modalities of therapy, the proposed mechanisms for asthma will be presented as distinct processes.

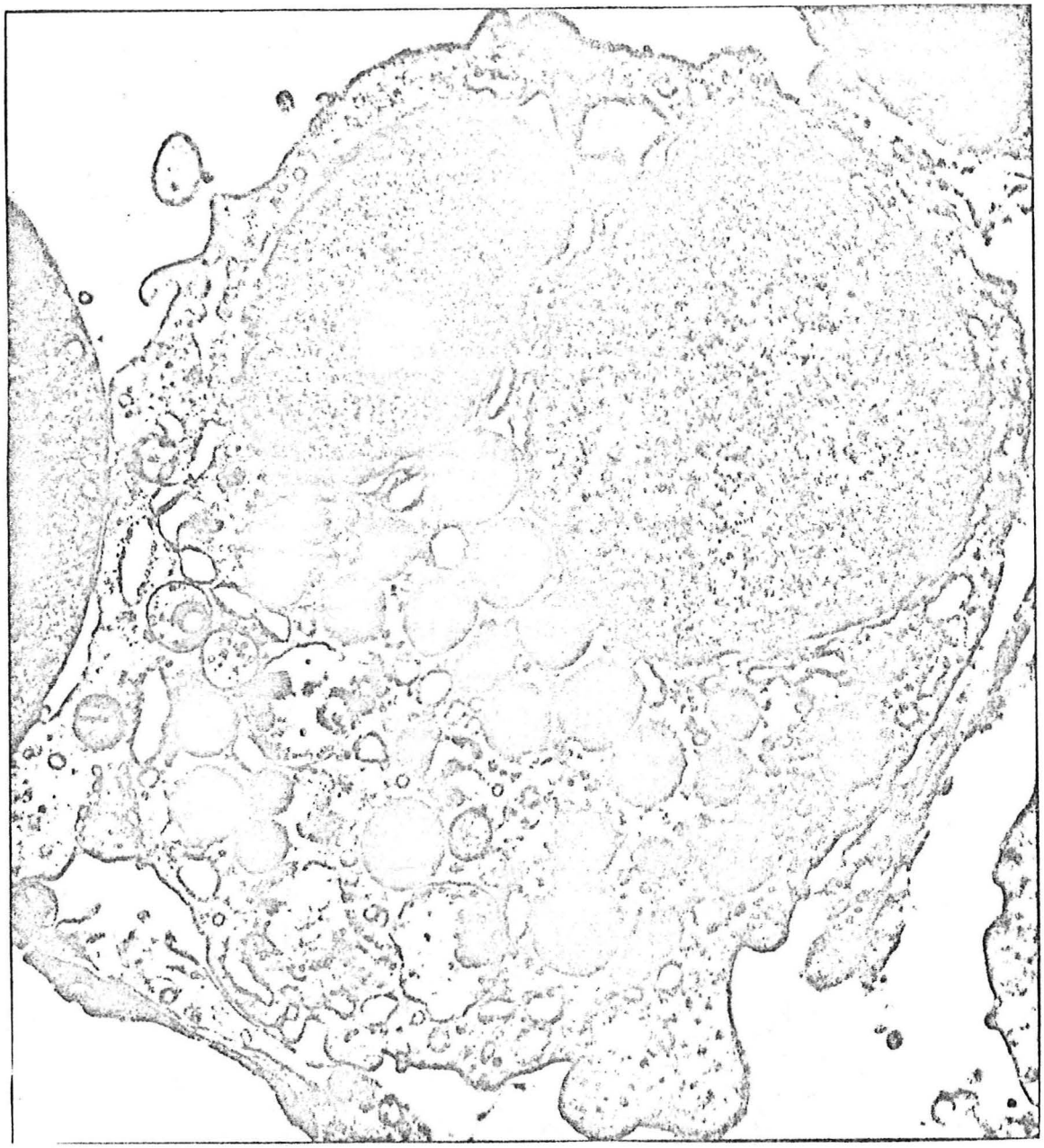
MECHANISMS OF ASTHMA

TABLE 1

THEORETICAL MECHANISMS OF ASTHMA

1. Mediator release
2. Increased parasympathetic activity
3. Abnormality of the adrenergic nervous system

Figure 1.

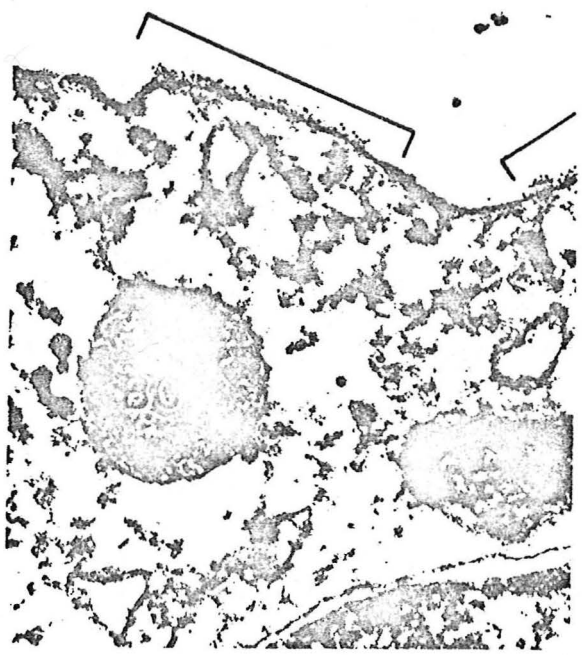


The mediator release mechanism was first proposed in 1910 (7) and is frequently referred to as the 'Classic Theory' of the cause of asthma. That increased parasympathetic activity might be a major cause of asthma was also proposed in 1910 (8), but there was little interest in or support for this mechanism until much more recently. An abnormality of the adrenergic nervous system in asthmatic persons was originally proposed in 1968 (9). I shall briefly summarize each of these without recounting specific investigations. During the review it will be apparent that these mechanisms are by no means mutually exclusive.

Mediator Release

The role of IgE in asthma has been elucidated primarily by the Ishizakas (10, 11). Recent studies on mediator release have been, in large part, carried out by Austen's group at Harvard (12, 13) and Lichtenstein's group at Johns Hopkins (14). This summary is a composite view of these investigators. The references are recent review articles, the bibliographies of which contain specific investigations leading to the current theory.

Figure 1.

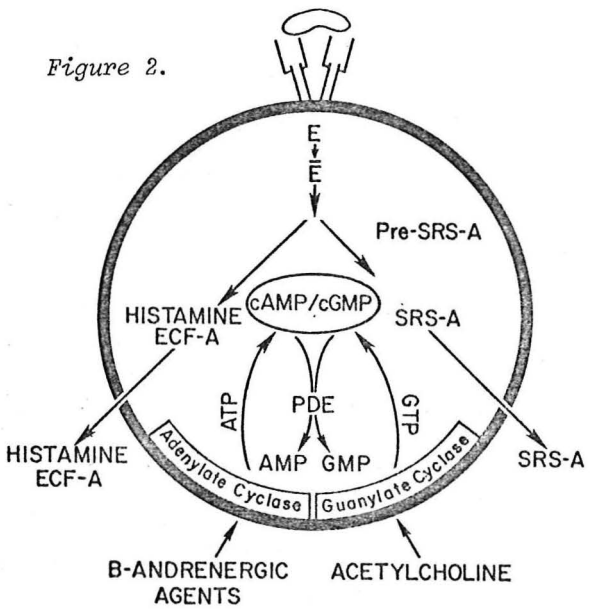


Electron micrograph of a basophil (left). These are the granules which contain histamine secreted as a result of an antigen-antibody interaction (X27,000). A close-up of the granules is seen above showing the actual IgE antibodies on the surface of the cell (X77,500). (Lichtenstein, Lawrence M.: Mediator release from basophils. In Asthma, Charles E. Reed and Sheldon C. Siegel, eds., MEDCOM, Inc., New York, p. 19.)

In the lung the mediators of asthma are contained in mast cells, although circulating basophils also contain the same mediators and may play some role. Mast cells are ubiquitous in the lung and are found especially in connective tissue septa in the peribronchial and perivascular regions (25). Their dense, metachromatically staining, cytoplasmic granules contain histamine, heparin, protease, and serotonin. Allergic and non-allergic persons have similar numbers of these cells. However, in persons with allergic asthma, IgE antibodies fix to the cell surface membranes and render the cells reactive to antigen.

IgE antibodies are specific immunoglobulins formerly referred to as reaginic antibodies. They are produced by B lymphocytes with help from T lymphocytes in response to specific antigens which are simple proteins. Although IgG may be formed against the same antigen, the two antibodies are evidently formed by different B cells. Circulating IgE in infants is only 10% of adult levels, but even in normal adults IgE is present only in nanogram amounts. In atopic individuals serum IgE levels may reach 20 times normal. In an allergic person up to 10% of all IgE may be dedicated to a single antigen.

Figure 2.



A single mast cell may have up to 90,000 receptor sites for IgE antibodies on the cell membrane. The IgE binds through its Fc portion in a reversible way to the cell, but this interaction is incompletely understood. Up to 40,000 IgE molecules may be attached to a single mast cell or basophil. When the antigen, or allergen, to which the

IgE is dedicated comes in contact with the antibody coated cell, it may bridge across and be bound to two IgE antibodies. The interaction of the two IgE molecules, the antigen, and the mast cell activates the ultimate generation and release of mediators of asthma. Activation is poorly understood but apparently involves activation of a proesterase (E) to an active serine esterase ($\bar{E}$).

Once activation of the sensitized mast cell has taken place two additional, interrelated steps occur. These are 1) generation of at least two mediators by the cell and 2) the release of these newly formed mediators and of at least three additional mediators which had been preformed and stored in the cell. Both generation and release are energy dependent and, like other cellular secretory functions, are modulated by the intracellular concentration of cyclic 3', 5'-adenosine monophosphate (cyclic AMP). The higher the level of cyclic AMP, the less mediator release occurs. Cyclic AMP is formed from adenosinetriphosphate (ATP) by activation of adenyl cyclase and is broken down by phosphodiesterase. Thus, agents which stimulate adenyl cyclase, such a β adrenergic drugs, or which inhibit phosphodiesterase, such as methylxanthines, inhibit mediator release. Conversely, agents which stimulate the α adrenergic system, such as norepinepherine, decrease cellular levels of cyclic AMP and potentiate mediator release.

In addition to the modulating effect of the adrenergic system, release of mediators evidently is partially controlled by the cholinergic system. Stimulation of cholinergic receptors by acetylcholine potentiates mediator release, but cyclic AMP is not involved. Acetylcholine acts to increase the intracellular level of cyclic guanozine 3', 5'-monophosphate (cyclic GMP) which enhances mediator release.

TABLE 2

MAST CELL RECEPTORS DETERMINING MEDIATOR RELEASE

Receptor	Action	Mediator Release
β adrenergic	↑ C AMP	↓
α adrenergic	↑ C AMP	↑
Cholinergic	↑ C GMP	↑
Prostaglandins, E series	↑ C AMP	↓
Prostaglandin $F_{2\alpha}$	↑ C AMP	↑
Histamine	↑ C AMP	↓

The mast cell has at least two additional receptors which modulate mediator release through cyclic AMP concentration. The prostaglandins have conflicting effects on mediator release much like the adrenergic system. The E series increases cyclic AMP and hence inhibit release, while prostaglandin $F_2 \alpha$ decreases cyclic AMP and thereby enhances release.

A histamine H_2 receptor has also been indentified on the mast cell. Histamine, one of the mediators released by the cell, may attach to this receptor, stimulate adenyl cyclase to increase cyclic AMP, and thereby inhibit further release of histamine. Thus, in allergic reactions, as in other biologic phenomena, an internal servomechanism feeds back to control the response.

TABLE 3.

MEDIATORS OF ASTHMA

Primary	Action
Preformed	
Histamine	↑ airway resistance & vascular permeability
ECF-A	attracts eosinophils
NCF-A	attracts neutrophils
Generated	
SRS-A	↑ airway resistance & vascular permeability
PAF	aggregates platelets
Kallikrein	forms bradykinin
Secondary	
Prostaglandins	↑ or ↓ airway resistance
Bradykinin	↑ airway resistance & vascular permeability

There are at least six mediators released from mast cells by the process described. Three of these, histamine, eosinophil chemotactic factor of anaphylaxis, (ECF-A), and neutrophil chemotactic factor of anaphylaxis (NCF-A) are stored in the cell before antigen activation. Two, slow reacting substance of anaphylaxis, SRS-A, and platelet activating factor, PAF, are generated and then released after cell activation. It is not known whether the sixth mediator, kallikrein,

is preformed or generated. Two additional potential mediators, prostaglandins and bradykinin, may be secondarily generated in the tissues surrounding the mast cell following release of the primary mediators.

Histamine, SRS-A, prostaglandin $F_{2}\alpha$, and bradykinin are all capable of increasing airways resistance by direct stimulation of the smooth muscle of the bronchi. Histamine, SRS-A, and bradykinin also increase the permeability of small blood vessels causing local edema. It is not clear which of these mediators may directly cause the third mechanism of airways obstruction, increased mucus production by bronchial glands.

ECF-A attracts and holds eosinophils to the area of mediator release. The function of these cells has not been completely elucidated. Recent work (16) suggests that eosinophils may release a preformed inhibitor which blocks the degranulation of mast cells and basophils, thus decreasing the allergic reaction. Alternately, eosinophils have been shown to contain aryl sulfatase, an enzyme capable of inactivating SRS-A. Neutrophil chemotactic factor attracts neutrophils which may add to local inflammation. The relevance of platelet aggregating factor to the pathogenesis of asthma remains unclear, and kallikrein activates bradykinin.

TABLE 4

SUMMARY OF THE MEDIATOR RELEASE THEORY

1. I_gE + antigen + mast cell cause release of preformed and newly generated mediators.
2. Mediators lead directly to bronchospasm, mucosal edema, and mucus production.

In summary, the mediator release theory postulates that cell attached IgE combines with specific antigens to activate mast cells and cause release of the preformed and newly generated mediators which have been enumerated. These mediators then act directly on the bronchial wall to lead to bronchospasm, mucosal edema, and excess mucus production.

Increased Parasympathetic Activity

Early work concerning the role of the vagus nerves in anaphylaxis or asthma was controversial, and reports of surgical denervation of the lungs of asthmatic patients performed by a variety of techniques were, in general, poorly documented. More recently Widdicombe and Nadel and their collaborators (17) have extensively studied the role of vagally mediated reflexes. Gold and his collaborators (18, 19) have extended these observations by experiments in asthmatic dogs and humans. The references are recent reviews of the concepts of these investigators, the bibliographies of which contain the specific work supporting their thesis.

Figure 3.

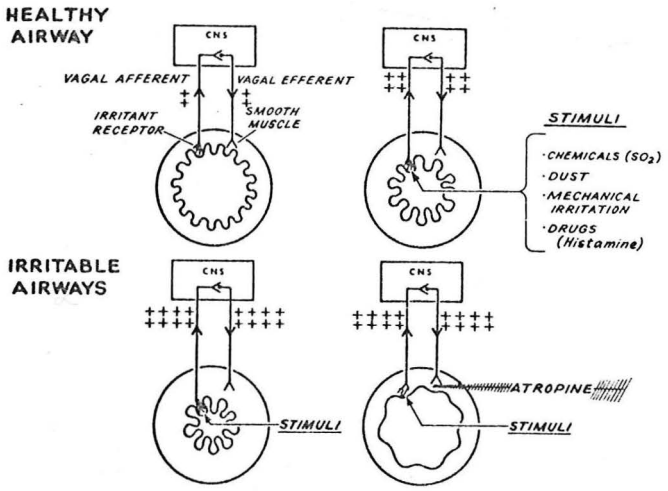


Diagram of hypothesis of irritant–bronchoconstrictor reflex. Circular structures represent airways and inner dimensions indicate degree of airway tone. Arrows indicate vagal reflex pathway from irritant receptor to central nervous system (CNS) to airway smooth muscle. Number of plus signs indicates relative frequency of firing of nerves. Upper left: healthy subject in control state shows mild degree of bronchoconstriction associated with slight nervous activity. Upper right: healthy subject during stimulation of irritant receptors shows increased bronchoconstriction compared to the control state associated with increased nervous activity. Lower left: patient with irritable airways during exposure to concentration of irritant similar to healthy subject shows more severe bronchoconstriction associated with marked stimulation of nervous pathways. Lower right: patient with irritable airways during stimulation of irritant receptors after atropine shows bronchodilatation in spite of continued nervous activity arising in irritant receptors.

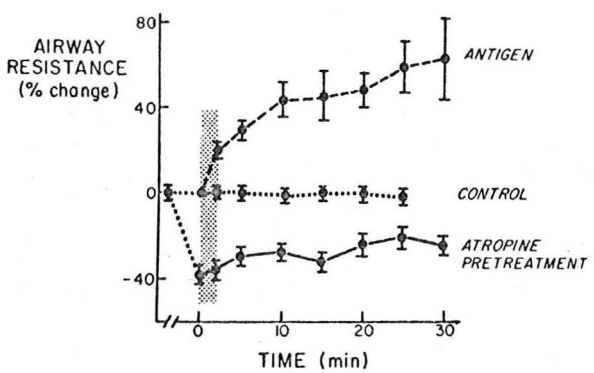
In normal humans and in experimental animals there is a mild degree of tone in airway smooth muscle maintained by vagal efferent nervous activity. Cutting the vagus nerve in animals or the administration of atropine to normal humans results in mild bronchodilatation. Stimulation of superficial airway receptors whose afferent and efferent

pathways are in the vagus nerves may reflexly alter airway smooth muscle tone. Stimulation of receptors in the larynx and large airways evokes cough, while stimulation of receptors in more peripheral airways evokes shallow breathing. Simultaneous stimulation results in bronchoconstriction which can be abolished by cutting the vagus nerves or by atropine sulfate.

Asthmatic persons develop bronchoconstriction when exposed to many non-immunological stimuli in concentrations which evoke no response in normal persons. These substances all stimulate the irritant receptors. In the asthmatic person the bronchoconstriction can be prevented by the prior administration of atropine.

Thus, it has been postulated that the abnormality in asthma may be an increased sensitivity of the airway receptors. Various mechanisms could explain an increased receptor sensitivity. Damage to the epithelium could partially depolarize the receptors and thereby decrease their threshold for firing. Alternately, histamine stimulates irritant receptors and if released from mast cells within airway tissues could decrease their firing threshold when other stimuli are introduced. The work of Gold, et al, in allergic dogs has strengthened the vagal theory by demonstrating that antigen induced asthma may be prevented by interruption of either vagal afferent or vagal efferent innervation.

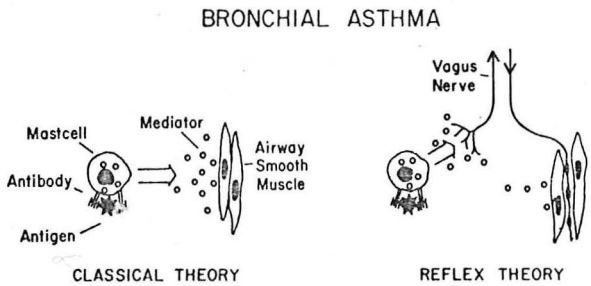
Figure 4.



Inhibition of antigen-induced bronchoconstriction in five asthmatic patients by intravenous atropine sulfate given before antigen inhalation. Each point represents the mean (·) ± SE (I). (---) Antigen aerosol alone (concentration was 1/10 that used when atropine was also given) ($n = 9$). (···) Control aerosol ($n = 16$) containing an antigen extract to which the patient was unreactive by history and skin test. (–) Antigen aerosol following atropine ($n = 7$). Ordinate: airway resistance (measured in a body plethysmograph) is expressed as a percentage change from control. Abscissa: the time from the start of the aerosol inhalation (stippled bar).

Yu, Galant, and Gold (20) have further investigated five asthmatic patients during antigen-induced bronchospasm. Following inhalation of an antigen aerosol there was a marked increase in airways resistance and the onset of clinical asthma. Pretreatment with 1.5 - 2.5 mgm of atropine sulfate intravenously, as shown in Figure 4, prevented the antigen-induced increase in airways resistance. In other studies, atropine administered after the onset of bronchospasm reversed the process. Interestingly, in two patients the IV atropine was not totally successful at blocking bronchospasm, but larger doses were precluded by systemic side effects. In these two patients atropine aerosol prior to antigen aerosol challenge prevented airways resistance from increasing above control values.

Figure 5.



The classical theory of asthma (left) suggests that antigen interacts with cell-fixed antibody to induce mediator release. The mediators of anaphylaxis, in turn, cause direct, local airway smooth muscle contraction. The concept cannot account for our results in experimental canine asthma nor the accumulating evidence from experiments in anaphylaxis as well as human asthma. The classical concept must be modified as indicated on the right. Antigen–antibody interaction may cause mediator release with direct, local contraction of the airway smooth muscle. But in the acute response to inhaled antigen this component is minor compared to a vagally mediated reflex bronchoconstriction. This reflex may result from stimulation of irritant receptors by the mediators, stimulation of the receptor by the antigen–antibody interaction itself, or stimulation secondarily after the mediators cause smooth muscle spasm and deformation of the receptors. Whatever the mechanism, it is clear that the parasympathetic nervous system is of central importance in the acute bronchoconstrictor response to inhaled antigen.

In summary, the classical theory suggests that antigen interacts with mast cells to cause mediator release. The mediators, in turn, cause direct, local airway smooth muscle contraction. The parasympathetic theory suggests that direct interaction bronchospasm is minor. Rather, the mediators mainly stimulate the mucosal irritant receptors which initiate a vagal reflex bronchoconstriction.

Abnormality of the Adrenergic Nervous System

TABLE 5

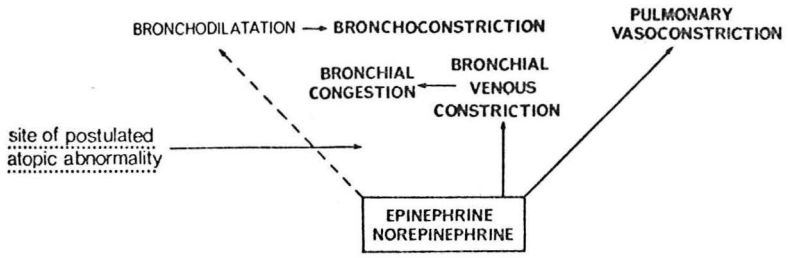
THE *Bordetella pertussis* ASTHMA MODEL

1. Hypersensitivity to histamine, serotonin, and bradykinin.
2. Hypersensitivity to non-specific stimuli like cold.
3. Reduced sensitivity to catecholamines.
4. Enhanced antibody (reagin) formation.
5. Marked eosinophilia.

During the 1960's Szentivanyi (9) and his colleagues worked with laboratory animals which had been injected with *Bordetella pertussis*, an organism known to produce a histamine-sensitizing factor (21). The principal features noted in their animals are indicated in Table 5.

These animals demonstrated hypersensitivity not only to endogenously released or exogenously administered mediators, but also to non-specific stimuli such as cold or respiratory irritants. In contrast, the animals had a reduced response to catecholamines. Additionally, there was a marked augmentation of antibody response to antigenic stimuli, and these antibodies had the properties of reagins. There was also a marked eosinophilia. Based on these experiments, Szentivanyi proposed that asthma is not an immunological disease but is a unique bronchial hyperreactivity due to adrenergic imbalance.

Figure 6.



Hypothetical schema of asthmatic responses to catecholamines under conditions of the postulated beta adrenergic blockade. Note the loss of adrenergic bronchodilator activity with subsequent prevalence of bronchial and venous constriction leading to airway obstruction.

The critical component of the malfunctioning system is viewed to be an inherited or acquired defect in beta adrenergic receptors. In this situation, the adrenergic neurotransmitters epinepherine and norepinephrine are released in the face of a relatively unavailable beta effector system and stimulate the unbalanced alpha adrenergic system causing bronchoconstriction and mucosal edema.

Szentivanyi considered respiratory infections as a likely cause of the beta adrenergic blockade by saturating or damaging the receptor-binding sites. It was felt that infections also could trigger prolonged firing of adrenergic neurons and thus precipitate overt clinical symptoms. The increasing evidence associating both the onset of asthma and the precipitation of attacks of asthma in children by viral infections (22-29) may support this thesis, although infections could certainly interact with the other theories of the pathophysiology of asthma.

In this model the ultimate effector of the increased airway resistance of the asthmatic patient is postulated to be alpha adrenergic stimulation. The importance of alpha receptors in this regard is controversial with evidence for (30-34) and against (35, 36) their playing a significant role. Since other mechanisms could effect bronchoconstriction in the presence of a beta blockade, some recent reviews have emphasized the evidence for the β receptor defect rather than α receptor stimulation (37, 38).

TABLE 6

In Vivo Response to Exogenously Administered β Stimulants

↑ Blood glucose	↑ Heart rate
↑ Blood lactate	↑ Cardiac output
↑ Serum free fatty acids	↓ Peripheral vascular resistance
↑ Urinary cyclic AMP	

Since the airways of normal persons respond very little to adrenergic stimulation, most studies assessing the β blockade theory *in vivo* have compared adrenergic responses between asthmatic and normal persons in extra pulmonary systems. Administration of a β stimulant should result in increases in blood glucose and lactate, serum free fatty acids and urinary cyclic AMP. Additionally, isoproteranol should increase the heart rate and cardiac output and decrease peripheral vascular resistance. Changes in the mean blood pressure depend on the magnitude of change of the other cardiovascular parameters. Several investigations of responses of these parameters to exogenously administered β stimulants have reported differing results (39-43). Some report that the response of asthmatic patients is less than normal, while others suggest it is normal. The resolution of these differences is not clear. However, the recent observations of Nelson and his colleagues (44) may be of considerable importance. They found that the response of normal persons to epinepherine infusions was significantly less following a week of ephedrine administration than it had been during control infusions. Since many of the asthmatic patients investigated by others were surely taking sympathomimetric drugs at the time of study, the response to β stimulation may have been spuriously depressed. An alternate explanation for variable results may be that not all asthmatics have the same defect, and β adrenergic blockage is not part of the pathogenesis of asthma in at least some patients (45, 46).

TABLE 7.

COMPARISON OF LEUKOCYTES OF ASTHMATIC TO NORMAL PERSONS

Decreased levels of cyclic AMP
Lesser increase of cyclic AMP by β agonists
Response of cyclic AMP worse with severe asthma
α adrenergic blocking agents augment response to β agonists

Because of the variability of *in vivo* findings, *in vitro* systems have been used to assess the β blockade theory. The most frequently reported assay is the measurement of leukocyte, or purified lymphocyte, cyclic AMP, since the cellular concentration is partially a function of β activity. A summary of the data supporting a β blockade is indicated in Table 7 (47-54).

Asthmatic patients have a decreased level of leukocyte cyclic AMP compared to normal persons, and there is a lesser increase in cyclic AMP when the cells are exposed to β agonists. These findings are more marked in patients with severe asthma, and cells from patients in remission may respond normally. Alpha adrenergic blocking agents may augment cellular response to β agonists. Although these data are considered definitive by proponents of the β blockade theory, a major problem not yet resolved is the effect of treatment of the asthmatic patients from whom the leukocytes are harvested.

An additional detraction from the *in vitro* studies is the single report (55) that the bronchi of asthmatic persons responded *in vitro* by a similar degree of relaxation as those of persons without asthma when each were exposed to isoproteranol.

TABLE 8.

SUMMARY OF β BLOCKADE THEORY

1. β adrenergic receptors of bronchial smooth muscle, vascular, and mast cells do not respond normally to endogenous or exogenous catecholamine stimulation.

2. Stimulation of the α adrenergic system by endogenous catecholamines (or perhaps cholinergic system) leads to asthma.

In summary, the β adrenergic blockade theory postulates that a congenital or acquired defect of β adrenergic receptors in bronchi causes them to not respond normally to endogenous or exogenous catacholamine stimulation. The unbalanced stimulation of the α adrenergic system by endogenous catecholamines, or perhaps the cholinergic system, leads to asthma.

THERAPEUTIC AGENTS

TABLE 9

RECENT ADVANCES IN THE THERAPY OF ASTHMA

	Mediators	Vagus	α Block
Clinically available			
Cromolyn	✓		
Theophylline	✓		✓
Selective β agonists	✓		✓
Topical (inhaled) steroids	?	?	?
Research only			
Atropine congeners	✓	✓	
α adrenergic blockers	✓		✓
Prostaglandin E	✓		✓
Vasoactive intestinal polypeptide	✓		✓

Many of the newer therapeutic agents used in the treatment of asthma could exert their effects through changes in more than one of the proposed mechanisms of asthma. Only cromolyn is known to have a single effect, blocking mediator release. Xanthines, old agents which are only recently being utilized to maximum effectiveness, and selective β agonists have traditionally been thought to act only on β receptors of smooth muscle and vascular cells, but it is apparent that they also could act by decreasing mediator release through raising mast cell cyclic AMP. The site of action of adenal corticosteroids is not known, but theoretically they could affect any of the systems that have been discussed (55). Since these agents are now clinically available, each will be discussed separately.

Additional agents are being actively investigated and may be available in the near future. One group of these, atropine and its congeners, has had a long history in the treatment of asthma. Atropine was introduced into England in 1802 (56) and evidently was widely used until about 1890 (57). For inapparent reasons it fell into disrepute, and it has been widely taught that atropine is contraindicated in asthma and chronic bronchitis because of its drying effects on bronchial mucous secretions. Sporadic reports of its bronchodilating effect on a single dose basis have continued (56, 57). It has been suggested as an agent to separate allergic from other forms of asthma, since it was thought not to prevent antigen or histamine induced bronchospasm (58). This finding is now a matter of some controversy (20, 59, 60). The recent renewal of interest in the role of the vagus in asthma (17-19) has prompted new clinical trials of atropine in chronic bronchitis (61) and asthma (62), and favorable results may occur for up to three weeks. Additionally, newer congeners with fewer systemic side effects are under investigation. At present, however, insufficient evidence is available to use atropine in the clinical management of patients.

Since α adrenergic stimulation decreases the concentration of cyclic AMP in both mast cells and bronchial smooth muscle, it may interact with at least two of the theories of asthma. The *in vitro* effects of α stimulation result in potentially detrimental consequences, and hence α adrenergic blockade could be beneficial to the asthmatic patient. Since the *in vivo* experimental results to date have been contradictory (30-36), the use of α adrenergic blockers still must be considered experimental.

Prostaglandins of the E series stimulate adenyl cyclase through receptors different from the β receptors and could thereby cause decreased mediator release and bronchodilatation. The latter has been demonstrated *in vivo* (63-64). Prostaglandin E_2 by inhalation has approximately the same bronchodilating effect in asthmatic patients as isoproteranol. At present, however, preparations of PGE_2 are extremely irritating to the pharynx and trachea and lead to coughing and mucus production. Whether prostaglandins will ever be useful clinically is not clear at present.

An additional potentially useful bronchodilator is the vasoactive intestinal polypeptide described by Dr. Sami I. Said (65). It is a potent stimulant of adenyl cyclase in several systems, but it has not yet been evaluated for clinical medicine.

Cromolyn

TABLE 10

PHARMACOLOGY OF CROMOLYN

White, crystalline powder of the chromone class.
Not absorbed from gastrointestinal tract.
Approximately 8% of inhaled dose absorbed.
Excreted unchanged in urine and bile.
Effective in prevention of mediator release.

The most novel of the newer anti-asthma drugs is cromolyn sodium (disodium cromoglycate; Trade names, Intal and Aarane) which was synthesized by workers at Fisons Pharmaceuticals (66-68). It is a white, crystalline powder with a slightly bitter taste which is of the chromone class of compounds. It is not metabolized in nor significantly absorbed from the gastrointestinal tract, and hence it is clinically useful only when administered by inhalation. Approximately 8% of an inhaled dose is absorbed from the lungs with peak blood levels in about 15 minutes. Ninety percent is excreted unchanged in urine and bile within six hours. Cromolyn has no demonstrable effect on the sympathetic or parasympathetic nervous systems, tracheobronchial mucus flow, attachment of IgE to mast cells, or blocking of the effects of mediators if already released from mast cells (68-72). It is not a bronchodilator. Its action is to prevent mediator release. Cromolyn evidently prevents mediator release due to non-immunological as well as immunological causes, since it may prevent exercise induced asthma when given before the onset of exercise (73, 74).

TABLE 11

CLINICAL RESULTS FROM CROMOLYN

Up to 80% favorable response.
Response only occasionally dramatic.
Beneficial in all types of asthmatics.
Better response in young patients.
Toxicity minimal.

Very extensive clinical trials involving thousands of patients have been carried out to evaluate the clinical efficacy of cromolyn (75-97). The measurement of the impact of any new treatment on this variable syndrome which usually must be treated with multiple drugs is difficult (98), and the clinical trials of cromolyn certainly reflect such problems. Nevertheless, some general conclusion may be drawn.

Up to 80% of patients report a favorable response to the drug in double blinded trials. The favorable results include stability or improvement of symptoms while using fewer other antiasthmatic drugs including steroids. Indeed, a major part of cromolyn's benefit is a reduction in steroid dosage. Many patients report increased exercise tolerance and decreased lability in their disease. However, only occasionally is the response to cromolyn dramatic enough to completely supress asthma without the use of other drugs.

Most series report that cromolyn is most likely to be effective in allergic asthma of either the seasonal or perennial type. Further, a favorable response is most likely to occur in children and young adults. However, it is clear that some fraction of patients with no allergic component to their asthma and some fraction of elderly patients will respond, and it is recommended that it be evaluated by a clinical trial in all asthmatics. It should be emphasized that it is of no benefit to patients with chronic bronchitis who do not have a clear-cut asthmatic component to their disease.

Side effects are minimal. Some patients complain of throat irritation, and an asthmatic attack may be precipitated by the inhalation of cromolyn in an occasional patient. The latter may be managed by pre-treatment with an inhaled bronchodilator. The only real toxicity of

which I am aware is the report of two cases of pulmonary infiltrates with eosinophilia while taking the drug (99, 100). Both patients recovered promptly with discontinuance of cromolyn and with steroid therapy.

TABLE 12

PRACTICAL ASPECTS OF CROMOLYN THERAPY

Administered by special 'Spinhaler'.
Standard dosage of 20 mg (1 cap) qid.
Use for prophylaxis only.
Results, if any, require 2-4 weeks.
Adjunctive therapy, remove other drugs slowly.

The drug must be administered as a powder in order to allow a large enough deposition by inhalation within a reasonable treatment interval. Thus, it cannot be administered by standard nebulizers; a special powder dispensing 'Spinhaler' is required. A standard dose of 20 mg (one capsule) is inhaled four times a day irrespective of age or body size.

It is important to emphasize that cromolyn is of benefit for prophylaxis only and is of no benefit in treatment of existing episodes of asthma. It is recommended that it be started when the patient is as stable as possible, since tracheobronchial deposition is impaired if a large volume of mucus is present. If improvement occurs, it will usually do so within 2-4 weeks of therapy. It is probably not reasonable to persist for longer intervals if symptomatic improvement is not apparent. However, if improvement has occurred, results may become progressively better over the next several months. Cromolyn should be viewed as adjunctive therapy, and other anti-asthmatic drugs, especially steroids, should be decreased cautiously.

TABLE 13

PHARMACOLOGY OF THEOPHYLLINE

Anhydrous theophylline the active agent.
Absorption probably similar for most patients.
Metabolism approximately 90% hepatic.
Serum half-life exceedingly variable.
Bronchodilator effect related to serum concentration.
Toxicity related to serum concentration.

Theophylline was introduced for the therapy of asthma in the 1930's, but the clinical pharmacology of the drug was not investigated thoroughly until the 1970's (101-106). It is now clear that, no matter which salt of theophylline is used, it is the free anhydrous theophylline that is the active agent. Absorption from the gastrointestinal tract is probably similar for most patients. The particular salt of theophylline administered does not affect the amount or rate of absorption, and peak plasma levels are reached in about one hour. Alcoholic and aqueous solutions probably allow more rapid absorption. More recently, microfine crystals of anhydrous theophylline have enabled more adequate solubilization for rapid absorption, and special tablet compounding techniques have provided slow release drug. Absorption is impeded by food in the gastrointestinal tract, so the drug should be administered before rather than after meals. Rectal suppositories are no longer advised owing to exceedingly variable absorption.

Approximately 90% of the drug is metabolized by the liver while 10% is excreted unchanged in the urine. Thus, liver disease markedly prolongs the serum half-life and necessitates adjustments in dosage. Hepatic metabolism is exceedingly variable. Although the mean serum half-life is around five hours, five-fold variability may be found in normal adults. Metabolism in children is usually faster than in adults, but considerable variability exists. It is now known what causes such variability, but it has been empirically observed that the plasma half-life of theophylline is shorter in cigarette smokers. The extreme variability in plasma half-lives among patients makes individualization of dosage of theophylline mandatory. Both the bronchodilating effect and toxicity are related to the serum concentration.

TABLE 14

RELATION BETWEEN PLASMA THEOPHYLLINE CONCENTRATIONS AND CLINICAL EFFECTS

Concentration g/ml	Efficacy	Toxicity
5 }	Minimal	
10 }	Optimal	
20		Gastrointestinal upset and nervousness
40		Arrhythmia
60		Convulsions

Minimal bronchodilatation may be seen at very low blood levels (107), but optimal effects are not observed until 10-20 µg/ml levels are achieved. At higher plasma concentrations bronchodilation may be better, but progressive side effects occur. Most commonly the first toxicity observed is gastrointestinal upset and nervousness with more serious toxicity such as arrhythmias or convulsions only at greater concentrations. Rarely, however, the more serious side effects preceed nausea, and convulsions have occurred at a plasma concentration of 25 µg/ml (108).

TABLE 15

INTRAVENOUS DOSES OF AMINOPHYLLINE

	Loading (mg/kg 1st 20 min)	Maintenance (mg/kg/hour)	Plasma Theophylline µg/ml
Children			
Initial	6	1.10	10 (5-15)
Second	3	1.65	15 (10-20)
Adults			
Initial	6	0.90	10 (5-15)
Second	3	1.35	15 (10-20)

For acutely ill asthmatics who do not respond to the aerosol administration of a β adrenergic agonist or perhaps to subcutaneous epinepherine administration, the intravenous use of aminophylline is indicated. Reasonable intravenous doses have been suggested by Piafsky and Ogilvie (106); these recommendations agree closely with those of Jenne (105).

A loading dose of 6 mg per kg of patient weight is administered over a 20 minute interval; in adults this is followed by a continuous maintenance infusion of 0.9 mg/kg/hour and in children by 1.1 mg/kg/hr. If the patient does not respond to this therapy by a lessening of symptoms, and if no side effects exist, an additional loading dose of 3 mg/kg is administered over 20 minutes, and the continuous infusion is increased to 1.35 mg/kg/hr in adults or 1.65 mg/kg/hr in children.

It should be emphasized that these dosage schedules are helpful in achieving the desired plasma concentration, but they are estimates at best. It has been demonstrated that either inadequate blood levels or overdosage with toxicity may result (109). The only reliable guide to therapy is monitoring the plasma theophylline concentration.

TABLE 16

ADJUSTMENTS IN INTRAVENOUS DOSES OF AMINOPHILLINE

Clinical Situation	Loading	Maintenance
Previous oral theophylline	½	usual
Congestive heart failure	usual	2/3
Severe liver disease	usual	½

An adjustment in dose is clearly indicated in some clinical situations. If the patient has taken oral theophylline, the loading dose is reduced in half, and the usual maintenance dose is administered. Since theophylline is inactivated by the liver, persons with an edematous liver from congestive heart failure should have the maintenance infusion reduced to 2/3 of the usual dose. Persons with severe liver disease should have the maintenance infusion reduced to 1/2 of the usual dose.

TABLE 17

AVAILABLE THEOPHYLLINE IN ORAL PREPARATIONS

Salt of Theophylline	Percent Anhydrous Theophylline
Aminophylline	85
Oxtriphylline	64.5
Theophylline sodium glycinate	50
Theophylline calcium salicylate	48

Guidelines also are becoming available for oral theophylline therapy. In using these, however, it must be remembered that the active agent is the free anhydrous theophylline. The percent of free drug varies considerably depending on which salt is being utilized (110). Thus the physician must know the type of salt of theophylline in the preparation dispensed in order to know the amount of effective drug that is being administered. Since there is no evidence that one salt of theophylline has an advantage over others, the use of the most active, least expensive aminophylline seems reasonable.

TABLE 18

ORAL DOSES OF AMINOPHYLLINE

Subjects	Aminophylline mg/kg/6 hrs	Plasma Theophylline Maximum/Minimum µg/ml	
Children			
Initial	5	7 (3-12)	2 (1- 6)
Optimal	8	12 (9-25)	4 (2-10)
Adults			
Initial	3	7 (4-12)	3 (1- 4)
Optimal	6	14 (10-24)	6 (3-16)

Expected plasma levels resulting from oral theophylline are indicated in Table 18 (106). It is clear that the exceedingly variable half-lives of the drug from patient to patient result in markedly different plasma concentrations for the same dose of medicine. Thus, it is wise to begin with a relatively small dose that is unlikely to lead to toxicity and progressively increase the dose until beneficial or side effects occur. Plasma theophylline concentration measurements are desirable in difficult management problems, if possible. The drug should be administered on a six hourly basis instead of a routine four times a day. Adjustments in dose should be made only every 2-3 days to allow a new steady state to occur.

It should be emphasized that the dose of theophylline must be individualized for each patient. Combination preparations that contain theophylline and ephedrine do not allow such individualization because of the side effects produced by the ephedrine. Thus, combination preparations usually are not warranted.

Selective β Agonists

TABLE 19

CLASSIFICATION OF β ADRENERGIC RECEPTORS

β_1 Receptors	
	↑ force and rate of cardiac contraction.
	Dilation of coronary arteries.
	Relaxation of alimentary tract.
β_2 Receptors	
	Dilation of bronchi, blood vessels, and uterus.
	Skeletal muscle tremor.

Additional progress has been made in the treatment of asthmatic patients by the availability of new, synthetic β adrenergic agonists which are more potent bronchodilators than cardiac stimulants. Lands and his colleagues first synthesized isoetherine and found it to be at least ten times more active on bronchial muscle than on heart muscle in *in vitro* preparations (111-114). This work was supported by observations in humans (115). These investigations led the Lands' group to propose

that there are two types of β receptors which they called β_1 and β_2. Although the original evidence for this hypothesis was not altogether convincing, it has now been accepted in whole or part by most clinical pharmacologists (116-121). According to this theory, stimulation of β_1, receptors results in an increase in the force and rate of cardiac contraction, dilation of the coronary arteries, and relaxation of the alimentary tract. Stimulation of β_2 receptors results in dilation of bronchi, blood vessels, and the uterus and decreased twitch tension of skeletal muscle which may lead to muscle tremor. Thus, it is potentially possible to cause bronchodilatation, a β_2 function, without cardiac stimulation, a β_1 function.

In applying this concept to the treatment of asthmatic patients certain precautions are necessary. First, no agonist yet synthesized is a pure β_2 stimulant. Although the newer bronchodilators have less potential for cardiac stimulation, all thus far described produce tachycardia and presumably changes in myocardial contractility. Second, β_2 stimulants may cause a decrease in peripheral vascular resistance and thereby alter myocardial function reflexly. Third, effects in humans are not always predictable from *in vitro* studies; the results of clinical trials are more significant for clinicians.

TABLE 20

BETA ADRENERGIC AGONISTS

Generic Name (British)	U.S. Trade Name
Epinepherine	Many
Isoproteranol (Isoprenaline)	Many
Isoetharine	Bronkosol
Metaproteranol (Orciprenaline)	Alupent, Metaprel
Terbutaline	Brethine, Bricanyl
Fenoterol	Berotec
Salbutamol, Albuterol	Proventil, Ventolin

The β agonists which are currently, or soon will become, commercially available in this country are indicated in Table 20. Of the two established bronchodilators, isoproteranol is generally considered more potent than the only naturally occurring catecholamine bronchodilator epinepherine (122).

Isoproterenol stimulates both β_1 and β_2 receptors equally and thus has appreciable cardiovascular effects. Since it is absorbed from the lung when given by inhalation, it may produce tachycardia or arrhythmias at bronchodilating doses. However, this potential probably has been over-emphasized, and it is not likely to cause serious difficulty in this regard (123, 124), especially at the small doses necessary to achieve maximal bronchodilatation (125). Isoproteranol is rapidly metabolized by bronchial cells causing it to have a short duration of action, on the order of two hours. Its tendency to be absorbed from the lung also decreases its duration of action, and some preparations contain a vasoconstrictor such as phenylephrine to delay absorption. This may (126) or may not (127) be clinically useful. Isoproteranol is rapidly metabolized in the stomach, and hence oral preparations are of no benefit.

Isoetharine, the first congener of isoproteranol, was the drug on which the β_1, β_2 hypothesis was based and showed significant selectivity of stimulation in animal studies. Although some clinical studies have suggested an *in vivo* advantage of isoetharine (128, 129), others have not been able to demonstrate such (130, 131). It is likely that to get an equal bronchodilating dose to that of isoproteranol results in an equal cardiac stimulation, although the duration of bronchodilatation is somewhat longer.

The first synthetic to depart from the catechol ring was a resorcinol derivative of isoproteranol, metaproteranol. This molecular change not only impedes metabolism and hence prolongs action in the lungs, but it also prevents metabolism in the stomach allowing the drug to be given orally. Metaproteranol demonstrates greater β_2 selectivity than previous drugs (122). It has on the order of 10-20 times less cardiac stimulation compared to isoproteranol (132, 133). When used by inhalation at a 1.5 mg dose it gives approximately equal early bronchodilatation as 1.0 mg of isoproteranol at a fraction of the increase in heart rate produced by the latter. Moreover, the effects are more prolonged, on the order of 3 to 4 hours. When given orally in 10 or 20 mg dosage, it has greater bronchodilating effects than 25 mg of ephedrine with fewer toxic effects (134). Its peak action orally is about 2 hours, and bronchodilation is maintained for at least 4 hours.

There have been two further modifications of the resorcinol structure, terbutaline and fenoterol. Terbutaline is available commercially at present while fenoterol has not yet cleared the FDA requirements. It is clear that these are more selective β_2 stimulants than isoproteranol and evidently more selective than metaproteranol, although like all β agonists thus far some cardiac stimulation occurs (135). Terbutaline by inhalation at 0.25 and 0.50 mg doses gives slightly less and slightly greater early bronchodilatation, respectively, than metaproteranol (136), and hence it is roughly equivalent to isoproteranol; it is still near maximal effectiveness at 5 hours. At this dose there is virtually no tachycardia. Terbutaline given by mouth has been shown to be an excellent drug with greater and longer lasting bronchodilatation than metaproteranol (137) or ephedrine (138-140). A

5 mg dose has an onset of action in 30 minutes and a duration of action of at least 7 hours; a higher dose produces more bronchodil tation but is associated with greater side effects (141). It has been administered in 5 mg three times a day dosage for up to one year without a decrease in effectiveness (142, 143). At this dose terbutaline causes a very slight increase in heart rate and a decrease in diastolic blood pressure. However, the most frequent and significant side effect is muscular tremor, especially in the hands. Tremor may be severe enough to prevent using the drug. However, the tremor tends to diminish with prolonged use, while bronchodilatation continues unchanged.

Salbutamol differs from the cathcholamines and resorcinol bronchodilators by being a saligenin derivative. Its properties are similar to the resorcinols in metabolism in the lung and stomach, so that it is long lasting when given by inhalation and may be given by mouth. It is approximately as active as isoproteranol as a bronchodilator but has only one-tenth the cardiac stimulating effect (144-146).

Salbutamol 0.2 mg by inhalation is a more potent bronchodilator than 1.5 mg of metaproteranol, and bronchodilatation remains maximal after 5 hours (147-149). At this dose there is virtually no cardiac stimulation. Orally, 5 mg of salbutamol has been shown to be comparable to 5 mg of terbutaline in every way (150). The maximal effect is in 2 to 6 hours and is sustained for at least 5 hours, the duration of the study. This dose produces very mild tachycardia. However, tremor is the most common complaint. Thus, salbutamol and terbutaline are apparently interchangeable drugs by inhalation or orally. It has been noted that in particular patients one drug may produce tremor while the other does not. If tremor is bothersome, it is reasonable to change drugs to determine if this side effect is less.

I am aware of no studies comparing the effects of the new β_2 agonists and oral theophylline. I also am not aware of studies to determine the potential synergistic effects of these drugs, although some patients have been maintained on full therapeutic doses of each without additive toxicity (151).

Topical Inhaled Steroids

TABLE 21

INHALED STEROIDS

Generic Name	U. S. Trade Name
Beclomethasone dipropionate	Vanceril
Triamcinolone acetonide	Aristocort ?
Betamethasone valerate	Valisone ?

Probably the most dramatic advance in the treatment of asthma has been the introduction of topically active, inhaled steroids. The use of a variety of inhaled steroid preparations had been attempted for 20 years, but absorption from the lung at doses necessary to prevent asthma had led to side effects similar to those observed with orally administered drugs. More recently beclomethasone, triamcinolone, and betamethasone have been demonstrated to be active locally at doses that do not cause sufficient absorption for systemic effects. Betamethasone and beclomethasone evidently produce similar effects at the same dose (152). On average, triamcinolone is used at a slightly higher dose (153-155), but experience with this more recent drug is limited. Only beclomethasone is presently available commercially.

TABLE 22

CLINICAL RESULTS FROM BECLOMETHASONE

Pituitary-adrenal suppression not present at doses lower than 1.6 mg daily.
Cessation or decrease in systemic steroids in approximately 80% of patients.
Young patients evidently respond better.
Beginning dose 2 inhalations (0.1 mg) 3 or 4 times a day.

Beclomethasone does not produce suppression of the pituitary-adrenal axis or systemic effects of steroids at doses below 1.6 mg daily (156-158), but doses above 1.0 mg in adults are not recommended. Approximately 80% of asthmatic patients who have been dependent on oral steroids can have cessation or decrease in systemic steroids (152, 159-166). Young patients evidently respond better than older patients. In those patients who do not respond, it has been suggested that large amounts of airway mucus prevents deposition on the mucosa. It also is likely that a poor response occurs in some patients because they do not use the freon powered inhalers properly. Observations of patients taking inhaled bronchodilators from metered freon dispensers indicate that a significant fraction cannot coordinate inhalation and hand action.

The usual beginning dose of beclomethasone in adults is 0.1 mg, 2 inhalations, 3 or 4 times a day. In children the beginning dose is approximately one-half of this amount. The dose is adjusted upward or downward slowly as necessary.

TABLE 23

PRECAUTIONS FOR INHALED STEROID THERAPY

Ineffective in status asthmaticus.
Sometimes necessary to initiate steroid therapy with oral or parenteral preparations.
Sometimes necessary to temporarily administer oral steroids during exacerbations.
Patients must be carefully instructed in use of metered, freon inhaler.

It must be emphasized that inhaled steroids should not replace parenteral or oral steroids for the acutely ill asthmatic. Deposition of the drug uniformly in the tracheobronchial tree may not be possible owing to poor distribution of ventilation. Similarly, it is sometimes necessary to initiate steroid therapy with oral or parenteral preparations even in less severely ill patients. In patients who are well controlled by inhaled steroids, it is sometimes necessary to temporarily administer oral steroids during an acute exacerbation while continuing the inhaled dose at a constant level.

All patients must be carefully instructed in the use of the metered, freon inhaler and should be observed while using it to insure compliance. The patient should breathe out toward residual volume. The dispenser is placed before a widely opened mouth and inspiration is started. The aerosol is activated just after the onset of inspiration, and the patient must continue to breathe in toward total lung capacity. The patient pauses at the end of inspiration for several seconds before exhaling. If the prescribed dose is more than one inhalation, such can be carried out after a few normal tidal volumes.

TABLE 24

COMPLICATIONS OF INHALED STEROID THERAPY

Up to 13% incidence of pharyngeal or laryngeal thrush.
Emergence of other allergies when systemic steroids discontinued.
Adrenal insufficiency.

A bothersome complication of inhaled steroid therapy in up to 13% of cases has been pharyngeal or laryngeal thrush. To my knowledge, no pulmonary or systemic candida infections have been reported. Thrush is dose related. It may respond to lowering the inhaled dose, but more frequently amphotericin lozenges have been successful. It may be necessary to reduce the dose of steroid in addition to the antifungal agent.

Another bothersome complication has been the emergence of other allergies when oral steroids are discontinued, despite adequate control of asthma. Such has been sufficiently severe in some patients to cause a return to oral therapy.

The final complication, adrenal insufficiency, cannot be overemphasized. Patients who have been on oral steroids will have suppression of the pituitary-adrenal axis which may require up to a year to recover (167). Since the inhaled drug gives no measurable steroid blood level, the patient whose oral preparation is stopped abruptly may have iatrogenic adrenal insufficiency. Typical withdrawal symptoms are fatigue, weakness, arthralgias, anorexia, nausea, desquamation of the skin, orthostatic dizziness, fainting, and hypoglycemia (168). During intervals of stress more serious cardiovascular manifestations may occur, and deaths have been reported from discontinuing oral drugs too precipitously in patients placed on inhaled steroids. Prolonged adrenal suppression may occur with as little as 15 mg of prednisone daily for two weeks or larger doses for shorter intervals (169).

REFERENCES

1. American Thoracic Society Statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases: Chronic Bronchitis, Asthma, and Pulmonary Emphysema. Amer. Rev. Resp. Dis. 85:762-768, 1962.

2. Rackemann, F. M.: Intrinsic asthma. J. Allergy Clin. Immunol. 11:147-162, 1940.

3. McDonald, James R., David A. Mathison, and Donald D. Stevenson: Aspirin intolerance in asthma. Detection by oral challenge. J. Allergy Clin. Immunol. 50:198-207, 1972.

4. Mathison, David A., Donald D. Stevenson, Eng M. Tan, and John H. Vaughn: Clinical profiles of bronchial asthma. J.A.M.A. 224:1134-1139, 1973.

5. Stevenson, Donald D., David A. Mathison, Eng M. Tan, and John H. Vaughn: Provoking factors in bronchial asthma. Arch. Int. Med. 135:777-783, 1975.

6. Vaughn, John H., and Carlos M. Arroyave: Emphasis for future research in asthma. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 525-536.

7. Dale, H. H., and P. P. Laidlaw: The physiological action of β-iminazolylethylamine. J. Physiol. (London) 41:318-344, 1910.

8. Auer, J., and P. A. Lewis: The physiology of the immediate reaction of anaphylaxis in the guinea pig. J. Exp. Med. 12: 151-175, 1910.

9. Szentivanyi, Andor: The beta adrenergic theory of the atopic abnormality in bronchial asthma. J. Allergy 42:203-232, 1968.

10. Ishizaka, Kimishige, and Teruko Ishizaka: Role of IgE and IgG antibodies in reaginic hypersensitivity in the respiratory tract. In Asthma: Physiology, Immunopharmacology, and Treatment, K. Frank Austen and Lawrence M. Lichtenstein, ed., Academic Press Inc., London, England, 1973, pp. 55-70.

11. Ishizaka, Kimishige: Function of IgE antibody and regulation of IgE antibody response. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 133-148.

12. Austen, K. Frank, and Robert P. Orange: State of the Art: Bronchial asthma: The possible role of the chemical mediators of immediate hypersensitivity in the pathogenesis of subacute chronic disease. Amer. Rev. Resp. Dis. 112:423-436, 1975.

13. Austen, K. Frank, Robert A. Lewis, Stephen I. Wasserman, and Edward J. Goetzl: Generation and release of chemical mediators of immediate hypersensitivity in human cells. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 187-209.

14. Lichtenstein, Lawrence M.: The control of IgE-mediated histamine release: Implications for the study of asthma. In Asthma: Physiology, Immunopharmacology, and Treatment, K. Frank Austen and Lawrence Lichtenstein, eds., Academic Press Inc., London, England, 1973, pp. 91-107.

15. Kleinermann, Jerome: Aspects of structure and ultrastructure of the lung as related to asthma. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 25-54.

16. Hubscher, T., and A. H. Eisen: A possible immunopharmacological role of human eosinophils in allergic reactions. In Mechanisms in Allergy, vol. 1: Reagin-Mediated Hypersensitivity, L. Goodfriend, A. H. Sehon, and R. P. Orange, eds., New York, Marcel Dekker, Inc., 1973, p. 413.

17. Nadel, Jay A.: Neurophysiologic Aspects of Asthma. In Asthma: Physiology, Immunopharmacology, and Treatment, K. Frank Austen and Lawrence Lichtenstein, eds., Academic Press Inc., London, England, 1973, pp. 29-37.

18. Gold, Warren M.: Cholinergic pharmacology in asthma. In Asthma: Physiology, Immunopharmacology, and Treatment, K. Frank Austen and Lawrence Lichtenstein, eds., Academic Press Inc., London, England, 1973, pp. 169-182.

19. Gold, Warren M.: Experimental Models of Asthma. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 241-249.

20. Yu, Donald Y. C., Stanley P. Galant, and Warren M. Gold: Inhibition of antigen-induced bronchoconstriction by atropine in asthmatic patients. J. Appl. Physiol. 32:823-828, 1972.

21. Munoz, J. and R. K. Bergman: Histamine-sensitizing factors from microbial agents, with special reference to *Bordetella pertussis*. Bacteriological Reviews 32 (2):103-126, 1968.

22. Ouellette, John J., and Charles E. Reed: Increased response of asthmatic subjects to methacholine after influenza vaccine. J. Allergy 36 (6):558-563, 1965.

23. Berkovich, S., S. J. Millian, and R. D. Snyder: The Association of viral and mycoplasma in infections with recurrence of wheezing in the asthmatic child. Ann. Allergy 28 (2):43-49, 1970.

24. Rooney, J. C., and H. E. Williams: The relationship between proved viral bronchiolitis and subsequent wheezing. J. Pediatrics 79(5):744-747, 1971.

25. Zweiman, Burton, William F. Schoenwetter, Joseph E. Pappano, Jr., Bruce Tempest, and Eugene A. Hildreth: Patterns of allergic respiratory disease in children with a past history of bronchiolitis. J. Allergy Clin. Immunol. 48(5):283-289, 1971.

26. McIntosh, Kenneth, Elliot F. Ellis, Leonard S. Hoffman, Tillinghast G. Lybass, Jerry J. Eller, and Vincent A. Fulginiti: The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. J. Pediatrics 82(4):578-590, 1973.

27. Minor, Theodore E., James W. Baker, Elliot C. Dick, Anthony N. DeMeo, John J. Ouellette, Marcus Cohen, and Charles E. Reed: Greater frequency of viral respiratory infections in asthmatic children as compared with their nonasthmatic siblings. J. Pediatrics 85(4):472-477, 1974.

28. Minor, Theodore E., Elliot C. Dick, Anthony N. DeMeo, John J. Ouellette, Marcus Cohen, and Charles E. Reed: Viruses as precipitants of asthmatic attacks in children. J.A.M.A. 227(3):292-298, 1974.

29. Minor, Theodore, Elliot C. Dick, James W. Baker, John J. Ouellette, Marcus Cohen, and Charles E. Reed: Rhinovirus and influenza type A infections as precipitants of asthma. Amer. Rev. Resp. Dis. 113:149-153, 1976.

30. Fleisch, Jerome H., Harriet M. Maling, and Bernard B. Brodie: Evidence for existence of alpha-adrenergic receptors in the mammalian trachea. Amer. J. Physiol. 218(2):596-599, 1970.

31. Kerr, James W., M. Govindaraj, and K. R. Patel: Effect of alpha-receptor blocking drugs and disodium cromoglycate on histamine hypersensitivity in bronchial asthma. Brit. Med. J. 2:139-141, 1970.

32. Bianco, S., J. P. Griffin, P. L. Kamburoff, and F. J. Prime: The effect of thymoxamine on histamine induced bronchospasm in man. Brit. J. Dis. Chest. 66:27-32, 1972.

33. Simonsson, B. G., N. Svedmyr, B. E. Skough, R. Anderson, and N. P. Bergh: In vivo and in vitro studies on receptors in human airways. Scan J. Resp. Dis. 53:227-236, 1972.

34. Gross, Gary N., Joseph F. Souhrada, and Richard S. Farr: The longterm treatment of an asthmatic patient using phentolamine. Chest 66(4):397-401, 1974.

35. Guirgis, H. M., and R. S. McNeill: The nature of the adrenergic receptors in isolated human bronchi. Thorax 24: 613-615, 1969.

36. Cabezas, G. A., P. D. Graff, and J. A. Nadel: Sympathetic versus parasympathetic nervous regulation of airways in dogs. J. Appl. Physiol. 31:651-655, 1971.

37. Parker, Charles: Adrenergic responsiveness in asthma. In Asthma: Physiology, Immunopharmacology, and Treatment, K. Frank Austen and Lawrence Lichtenstein, eds., Academic Press Inc., London, England, 1973, pp. 185-210.

38. Reed, Charles E.: Abnormal autonomic mechanisms in asthma. J. Allergy Clin. Immunol. 53:34-41, 1974.

39. Inoue, Shiro: Effects of epinephrine on asthmatic children. J. Allergy 40:337-348, 1967.

40. Grieco, Michael H., Richard N. Pierson, Jr., and F. Xavier Pi-Sunyer: Comparison of the circulatory and metabolic effects of isoproterenol, epinephrine and methoxamine in normal and asthmatic subjects. Amer. J. Med. 44:863-872, 1968.

41. Middleton, Jr., Elliott, and Stanley R. Finke, and Fanny Arce: Metabolic response to epinephrine in bronchial asthma. J. Allergy 42:288-299, 1968.

42. Lecks, Harold I., David W. Wood, and Gordon Donsky: The metabolic, circulatory, and bronchomotor responses of asthmatic children to epinephrine infusion. J. Allergy 44(5): 261-271, 1969.

43. Makino, Sohei, John J. Ouellette, Charles E. Reed, and Charles Fishel: Correlation between increased bronchial response to acetylcholine and diminished metabolic and eosinopenic responses to epinephrine in asthma. J. Allergy 46(3):178-189, 1970.

44. Nelson, Harold S., J. Waylon Black, L. Bernard Branch, Bruce Pfuetze, Harry Spaulding, Richard Summers, and Dale Wood: Subsensitivity to epinephrine following the administration of epinephrine and ephedrine to normal individuals. J. Allergy Clin. Immunol. 55(5):299-309, 1975.

45. Orehek, J., P. Gayrard, Ch. Grimaud, and J. Charpin: Effect of beta adrenergic blockade on bronchial sensitivity to inhaled acetylcholine in normal subjects. J. Allergy Clin. Immunol. 55(3):164-169, 1975.

46. Gayrard, Pierre, Jean Orehek, Charles Grimaud, and Jacques Charpin: Beta-adrenergic function in airways of healthy and asthmatic subjects. Thorax 30:657-662, 1975.

47. Logsdon, Patricia J., Elliott Middleton, Jr., and Ronald G. Coffey: Stimulation of leukocyte adenyl cyclase by hydrocortisone and isoproterenol in asthmatic and nonasthmatic subjects. J. Allergy Clin. Immunol. 50:45-56, 1972.

48. Parker, Charles W., and Jay W. Smith: Alterations in cyclic adenosine monophosphate metabolism in human bronchial asthma. I. Leukocyte responsiveness to β-adrenergic agents. J. Clin. Invest. 52:48-59, 1973.

49. Parker, Charles W., Mary G. Huber, and Mary L. Baumann: Alterations in cyclic AMP metabolism in human bronchial asthma. III. Leukocyte and lymphocyte responses to steroids. J. Clin. Invest. 52:1342-1348, 1973.

50. Logsdon, P. J., D. V. Carnright, E. Middleton, Jr., and R. G. Coffey: The effect of phentolamine on adenylate cyclase and on isoproterenol stimulation in leukocytes from asthmatic and nonasthmatic subjects. J. Allergy Clin. Immunol. 52: 148-157, 1973.

51. Gillespie, Elizabeth, Martin D. Valentine, and Lawrence M. Lichtenstein: Cyclic AMP metabolism in asthma: Studies with leukocytes and lymphocytes. J. Allergy Clin. Immunol. 53(1):27-33, 1974.

52. Coffee, Ronald G., John W. Hadden, and Elliott Middleton, Jr.: Increased adenosine triphosphatase in leukocytes of asthmatic children. J. Clin. Invest. 54:138-146, 1974.

53. Alston, W. C., K. R. Patel, J. W. Kerr: Response of leukocyte adenyl cyclase to isoprenaline and effect of alpha-blocking drugs in extrinsic bronchial asthma. Brit. Med. J. 1:90-93, 1974.

54. Svedmyr, Nils L. V., Sven A. Larsson, and Gunnar K. Thiringer: Development of "resistance" in beta-adrenergic receptors of asthmatic patients. Chest 69:479-483, 1976.

55. Middleton, Jr., Elliott: Mechanism of Action of Corticosteroids. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 433-446.

56. Chamberlain, D. A., D. C. F. Muir, and K. P. Kennedy: Atropine methonitrate and isoprenaline in bronchial asthma. Lancet 2:1019-1021, 1962.

57. Herxheimer, H.: Atropine cigarettes in asthma and emphysema. Brit. Med. J. 2:167-171, 1959.

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

59. Itkin, Irving H., and Suresh C. Anand: The role of atropine as a mediator blocker of induced bronchial obstruction. J. Allergy 45:178-186, 1970.

60. Drazen, Jeffrey M.: In vivo effects of humoral mediators. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 251-259.

61. Klock, Lawrence E., Terry D. Miller, Alan H. Morris, Suetaro Watanabe, and Marian Dickman: A comparative study of atropine sulfate and isoproterenol hydrochloride in chronic bronchitis. Amer. Rev. Resp. Dis. 112:371-376, 1975.

62. Cropp, Gerd J. A.: The role of the parasympathetic nervous system in the maintenance of chronic airway obstruction in asthmatic children. Amer. Rev. Resp. Dis. 112:599-605, 1975.

63. Cuthbert, M. F.: Effect on airways resistance of prostaglandin E_1 given by aerosol to healthy and asthmatic volunteers. Brit. Med. J. 4:723-726, 1969.

64. Smith, A. P.: Role of prostaglandins in the pathogenesis and treatment of asthma. In Asthma: Physiology, Immunopharmacology, and Treatment, K. Frank Austen and Lawrence Lichtenstein, eds., Academic Press, Inc., London, England, 1973, pp. 267-277.

65. Said, Sami I.: Humoral mediators in bronchial asthma: Implications for therapy. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 261-273.

66. Cox, J. S. G.: Disodium cromoglycate (FPL 670) ('Intal'*): A specific inhibitor of reaginic antibody-antigen mechanisms. Nature 216:1328-1329, 1967.

67. Altounyan, R. E. C.: Inhibition of experimental asthma by a new compound--disodium cromoglycate "Intal". Acta Allergy 22:487, 1967.

68. Cox, J. S. G.: Disodium cromoglycate. Mode of action and its possible relevance to the clinical use of the drug. Brit. J. Dis. Chest 65:189-204, 1971.

69. Orange, R. P., and K. F. Austen: Pharmacologic dissociation of immunologic release of histamine and slow reacting substance of anaphylaxis in rats. Proc. Soc. Exp. Biol. Med. 129:836-841, 1968.

70. Blair, A. M. J. N. and Audrey Woods: The effects of isoprenaline, atropine and disodium cromoglycate on ciliary motility and mucous flow measured in vivo in cats. Brit. J. Pharmacol. 35:379-380, 1969.

71. Assem, E. S. K. and J. L. Mongar: Inhibition of allergic reactions in man and other species by cromoglycate. Int. Arch. Allergy 38:68-77, 1970.

72. Molk, Leizer: Blocking of induced asthma by cromolyn sodium. Ann. Allergy 30:321-325, 1972.

73. Davies, S. E.: Effect of disodium cromoglycate on exercise-induced asthma. Brit. Med. J. 3:593-594, 1968.

74. Poppius, H., A. Muittari, K. E. Kreus, O. Korhonen, and A. Viljanen: Exercise asthma and disodium cromoglycate. Brit. Med. J. 4:337-339, 1970.

75. Howell, J. B. L. and R. E. C. Altounyan: A double-blind trial of disodium cromoglycate in the treatment of allergic bronchial asthma. Lancet 2:539-542, 1967.

76. Grant, I. W. B., Sonia Channell, and J. C. Drever: Disodium cromoglycate in asthma. Lancet 2:673, 1967.

77. Kennedy, M. C. S.: Disodium cromoglycate in asthma. Lancet 2:838, 1967.

78. Pepys, J., Moira Chan, F. E. Hargreave, and D. S. McCarthy: Inhibitory effects of disodium cromoglycate on allergen-inhalation tests. Lancet 2:134-137, 1968.

79. Moran, F., Bankier, J. D. H., G. Boyd: Disodium cromoglycate in the treatment of allergic bronchial asthma. Lancet 2: 137-139, 1968.

80. Grant, I. W. B.: Disodium cromoglycate in bronchial asthma. Lancet 2:282, 1968.

81. Kidner, P. H., P. Meisner, N. B. Pride, and R. S. Bruce Pearson: Disodium cromoglycate in the treatment of bronchial asthma. Lancet 2:655-657, 1968.

82. Smith, J. Morrison, and G. F. Devey: Clinical trial of disodium cromoglycate in treatment of asthma in children. Brit. Med. J. 2:340-344, 1968.

83. Robertson, D. G., S. W. Epstein, and D. A. Warrell: Trial of disodium cromoglycate in bronchial asthma. Brit. Med. J. 1:552-554, 1969.

84. Herxheimer, H., and Helga Bewersdorff: Disodium cromoglycate in the prevention of induced asthma. Brit. Med. J. 2:220-222, 1969.

85. Read, John, and A. S. Rebuck: Steroid-sparing effect of disodium cromoglycate ("Intal") in chronic asthma. Med. J. Australia 1:566-569, 1969.

86. Campbell, Alastair H., and M. K. Tandon: A trial of disodium cromoglycate in older asthmatics. Med. J. Australia 2:535-537, 1969.

87. Ford, R. Munro: Disodium cromoglycate in the treatment of seasonal and perennial asthma. Med. J. Australia 2:537-540, 1969.

88. Lopez, Manuel, Francis C. Lowell, and William Franklin: A controlled study of disodium cromoglycate in the treatment of bronchial asthma. J. Allergy 44:118-121, 1969.

89. Anderson, J. R., et. al.: General Practitioner Clinical Trials. Disodium cromoglycate in asthma. Practitioner 203: 220-224, 1969.

90. Chen, Joyce L., Nicholas Moore, Philip S. Norman, and Thomas E. Van Metre, Jr.: Disodium cromoglycate, a new compound for the prevention of exacerbations of asthma. J. Allergy 43:89-100, 1969.

91. Chai, H., L. Molk, C. J. Falliers, and D. Miklich: Steroid-sparing effects of disodium cromoglycate (DSC) in children with severe chronic asthma. In Excerpta Medica International Congress Series No. 232: New Concepts in Allergy and Clinical Immunology, 1970, pp. 385-391.

92. Toogood, J. H., N. M. Lefcoe, D. K. Rose, and D. R. McCourtie: A double-blind study of disodium cromoglycate for prophylaxis of bronchial asthma. Am. Rev. Resp. Dis. 104:323-330, 1971.

93. Zwi, S., A. W. W. Van As, and H. I. Goldman: Disodium cromoglycate (Lomudal) in asthma with emphasis on lung function tests. S. A. Med. J. 45:823-827, 1971.

94. Burgher, Louis W., R. Michael Elliott, and Irving Kass: A perspective on the role of cromolyn soidum as an anti-asthmatic agent. Chest 60:210-213, 1971.

95. Bernstein, I. Leonard, et al.: A controlled study of cromolyn sodium sponsored by the Drug Committee of the American Academy of Allergy. J. Allergy Clin. Immunol. 50:235-245, 1972.

96. Irani, Furadoon A., Norman L. Jones, Michael Gent, and Michael T. Newhouse: Evaluation of disodium cromoglycate in intrinsic and extrinsic asthma. Amer. Rev. Resp. Dis. 106:179-185, 1972.

97. Crisp, J., C. Ostrander, A. Giannini, G. Stroup, and William C. Deamer: Cromolyn sodium therapy for chronic perennial asthma: a double-blind study of 40 children. J.A.M.A. 229:787-789, 1974.

98. Chai, Hyman, Kenneth Purcell, Kirk Brady, and C. J. Falliers: Therapeutic and investigational evaluation of asthmatic children. J. Allergy 41:23-36, 1968.

99. Lobel, H., I. Machtey, M. Y. Eldror: Pulmonary infiltrates with eosinophilia in an asthmatic patient treated with disodium cromoglycate. Lancet 2:1032, 1972.

100. Burgher, Louis W., Irving Kass, and Jerald R. Schenken: Pulmonary llergic ranulomatosis: a possible drug reaction in a patient receiving cromolyn sodium. Chest 66:84-86, 1974.

101. Jenne, J. W., E. Wyze, F. S. Rood, and F. M. MacDonald: Pharmacokinetics of theophylline: Application to adjustment of the clinical dose of aminophylline. Clin. Pharmacol. Ther. 13:349-360, 1972.

102. Mitenko, Paul A., and Richard I. Ogilvie: Rational intravenous doses of theophylline. N. Engl. J. Med. 289:600-603, 1973.

103. Ellis, Elliot F.: Asthma in childhood: Clinical pharmacology of theophylline in asthmatic children. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 317-323.

104. Miech, R. P., and S. M. Lohman: Metabolism and pharmacodynamics of theophylline. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 377-390.

105. Jenne, John W.: Rationale for methylxanthines in asthma. In New Directions in Asthma, Myron Stein, ed., Rahms in Lund, Sweden, 1975, pp. 391-413.

106. Piafsky, Kenneth M., and Richard I. Ogilvie: Drug Therapy. Dosage of theophylline in bronchial asthma. N. Engl. J. Med. 292:1218-1222, 1975.

107. Nicholson, David R., and Thomas W. Chick: A re-evaluation of parenteral aminophylline. Amer. Rev. Resp. Dis. 108:241-247, 1973.

108. Zwillich, Clifford W., Frank D. Sutton, Jr., Thomas A. Neff, Warren M. Cohn, Richard A. Matthay, and Miles M. Weinberger: Theophylline-induced seizures in adults. Correlation with serum concentrations. Ann. Int. Med. 82:784-787, 1975.

109. Weinberger, Miles W., Richard A. Matthay, Elliot J. Ginchansky, Charles A. Chidsey, and Thomas L. Petty: Intravenous aminophylline dosage. Use of serum theophylline measurement for guidance. J.A.M.A. 235:2110-2113, 1976.

110. Elliot, E. F., and E. D. Eddy: Anhydrous theophylline equivalence of commercial theophylline formulations. J. Allergy Clin. Immunol. 53:116-119, 1974.

111. Lands, A. M., F. P. Luduena, J. O. Hoppe, and Irene H. Oyen: The pharmacologic actions of the bronchodilator drug, Isoetharine. J. Amer. Pharm. Assoc. 47(10):744-748, 1958.

112. Lands, A. M., and Theodore G. Brown, Jr.: A comparison of the cardiac stimulating and bronchodilator actions of selected Sympathomimetic Amines. Proc. Soc. Exp. Biol. Med. 116: 331-333, 1964.

113. Lands, A. M., F. P. Luduena and H. J. Buzzo: Differentiation of receptors responsive to isoproterenol. Life Sci. 6:2241-2249, 1967.

114. Lands, A. M., A. Arnold, J. P. McAuliff, E. P. Luduena, and T. G. Brown, Jr.: Differentiation of receptor systems activated by sympathomimetic amines. Nature 214:597-598, 1967.

115. Collier, J. G., and A. C. Dornhorst: Evidence for two different types of β-receptors in man. Nature 223:1283-1284, 1969.

116. Brittain, R. T., D. Jack, and A. C. Ritchie: Recent β-adrenoreceptor stimulants. Adv. Drug. Res. 5:197-253, 1970.

117. Jack, D.: An introduction to salbutamol and other modern beta-adrenoreceptor stimulants. Postgrad. Med. J. 47:8-11, 1971.

118. Jack, David: Selectively acting β-adrenoreceptor stimulants in asthma. In Asthma: Physiology, Immunopharmacology, and Treatment, K. Frank Austen and Lawrence Lichtenstein, eds., Academic Press, Inc., London, England, 1973, pp. 251-266.

119. Caron, Mark G., and Robert J. Lefkowitz: Beta-adrenergic receptors: Basic studies and clinical implications. In New Directions in Asthma, Myron Stein, ed., Rahms, in Lund, Sweden, 1975, pp. 85-101.

120. Van As, Andre: Beta-adrenergic stimulant bronchodilators. In New Directions in Asthma, Myron Stein, ed., Rahms, in Lund, Sweden, 1975, pp. 415-432.

121. Lefkowitz, Robert J.: β-adrenergic receptors: Recognition and regulation. N. Engl. J. Med. 295(6):323-328, 1976.

122. Riding, W. D., P. Dinda, and S. S. Chatterjee: The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma. Br. J. Dis. Chest 64:37-45, 1970.

123. Assael, Roberto, J. M. Martt, and G. C. Okeson: Frequency of isoproterenol hydrochloride—induced cardiac arrhythmia in 19 patients with chronic obstructive pulmonary disease: A prospective study. Amer. Rev. Resp. Dis. 111:743-747, 1975.

124. Shim, Chang, and M. Henry Williams: Cardiac response to repeated doses of isoproterenol aerosol. Ann. Int. Med. 83(2):208-211, 1975.

125. Williams, M. Henry, and Cecelia Kane: Dose response of patients with asthma to inhaled isoproterenol. Amer. Rev. Resp. Dis. 111:321-324, 1975.

126. Cohen, A. A., and F. C. Hale: Comparative effects of isoproteranol aerosols on airway resistance in obstructive pulmonary diseases. Amer. J. Med. Sci. 249:309-315, 1965.

127. Grant, Joseph L., Norman Werfelman, Milton R. Cook, and William Metherall: Comparison of isoproterenol and isoproterenol-phenylephrine aerosols. Chest 60:129-132, 1971.

128. Unger, Donald L., and Leon Unger: Isoetharine methanesulfonate with phenylephrine hydrochloride and thenyldiamine (Bronkometer) in hypertensive and sympathomimetic amine-sensitive asthmatic patients. Dis. Chest 51(2):153-155, 1967.

129. Chervinsky, Paul, and Robert Herstoff: IPPB therapy with Bronkospray or Isoproterenol -- A comparison J. Asthma Res. 4(3):197-204, 1967.

130. Hoffbrand, B. I., M. I. Hoffbrand, I. D. Hill, and P. J. D. Heaf: Trial of bronchodilator drugs given by metered aerosol with a comparison of two bedside methods of estimating airway resistance. Brit. Med. J. 1:1014-1016, 1966.

131. Hemlich, Ernest M., and Robert E. Smith: Effects of isoprophenamine and methopyrilene in childhood asthma. Ann. Allergy 20:517-522, 1962.

132. Shanks, R. G., I. Brick, K. Hutchison, and I. C. Roddie: Stimulation of adrenergic β-receptors by orciprenaline. Brit. Med. J. 1:610-612, 1967.

133. McEvoy, J. D. S., A. Vall-Spinosa, and J. W. Paterson: Assessment of orciprenaline and isoproterenol infusions in asthmatic patients. Amer. Rev. Resp. Dis. 108:490-500, 1973.

134. Kennedy, M. C. S., and S. L. O. Jackson: Oral sympathomimetic amines in treatment of asthma. Brit. Med. J. 2:1506-1509, 1963.

135. Elgefors, Börje, and Lars Wilhelmsen: Effects of a new stimulator of beta-receptors, terbutaline, on ventilatory capacity, lung resistance, heart rate and blood pressure. European J. Clin. Pharmacol. 3:209-214, 1971.

136. Formgren, Hans: Clinical comparison of inhaled terbutaline and orciprenaline in asthmatic patients. Scand. J. Resp. Dis. 51:203-211, 1970.

137. Formgren, Hans: A clinical comparison of the effect of oral terbutaline and orciprenaline. Scand. J. Resp. Dis. 51: 195-202, 1970.

138. Dulfano, Mauricio J., and Paul Glass: Evaluation of a new B_2 adrenergic receptor stimulant, terbutaline, in bronchial asthma. II. Oral comparison with ephedrine. Current Therapeutic Research 15(4):150-157, 1973.

139. Tashkin, Donald P., Robert Meth, Daniel H. Simmons, and Y. Enoch Lee: Double-blind comparison of acute bronchial and cardiovascular effects of oral terbutaline and ephedrine. Chest 68:155-161, 1975.

140. Geumei, Aida, W. F. Miller, P. N. Paez, and L. R. Gast: Evaluation of a new oral β_2-adrenoceptor stimulant bronchodilator, terbutaline. Pharmacology 13:201-211, 1975.

141. Fagerberg, E., and K.-B. Tegner: Effects of oral terbutaline in asthmatic patients. A dose response study. Scand. J. Resp. Dis. 53:3-9, 1972.

142. Formgren, Hans: Experiences of longterm treatment of asthma with terbutaline: A study on frequency of side effects and therapeutic effect. Acta Allergologica 26:81-89, 1971.

143. Wilson, Archie F., Harold S. Novey, Paul Claninger, James Davis, and David White: Cardiopulmonary effects of long-term bronchodilator administration. J. Allergy Clin. Immunol. 58(1):204-212, 1976.

144. Warrell, D. A., D. G. Robertson, J. Newton Howes, M. E. Conolly, J. W. Paterson, L. J. Beilin, and C. T. Dollery: Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. Brit. Med. J. 1:65-70, 1970.

145. Simpson, W. T.: Initial studies on the human pharmacology of salbutamol. Postgrad. Med. J. 47:35-39, 1971.

146. Riding, W. D., S. S. Chatterjee, and P. Dinda: Clinical trial of a new β-adrenergic stimulant in asthma. Brit. J. Clin. Pract. 23:217-219, 1969.

147. Choo-Kang, Y. F. J., W. T. Simpson, and I. B. Grant: Controlled comparison of the bronchodilator effects of three β-adrenergic stimulant drugs administered by inhalation to patients with asthma. Brit. Med. J. 2:287-289, 1969.

148. Kennedy, M. C. S., and W. T. Simpson: Human pharmacological and clinical studies on salbutamol: A specific β-adrenergic bronchodilator. Brit. J. Dis. Chest 63:165-174, 1969.

149. Racoveanu, Carmen, Dan C. Stănescu, Mihai Manicatide, and Valentine Stroescu: The bronchodilator effects of orciprenaline and salbutamol. A double-blind study. Postgrad. Med. J. (Suppl.) 47:83-86, 1971.

150. Legge, J. S., J. Gaddie, K. N. V. Palmer: Comparison of two oral selective β_2-adrenergic stimulant drugs in bronchial asthma. Brit. Med. J. 1:637-639, 1971.

151. Jenne, John W. (Personal communication).

152. McAllen, M. K., S. J. Kochanowski, and K. M. Shaw: Steroid aerosols in asthma: An assessment of betamethasone valerate and a 12-month study of patients on maintenance treatment. Brit. Med. J. 1:171-175, 1974.

153. Williams, Jr., M. Henry, Cecelia Kane, and Chang S. Shim: Treatment of asthma with triamcinolone acetonide delivered by aerosol. Amer. Rev. Resp. Dis. 109:538-543, 1974.

154. Williams, Jr., M. Henry: Corticosteroid aerosols for the treatment of asthma. J.A.M.A. 231(4):406-407, 1975.

155. Kriz, Robert J., Frank Chmelik, Guillermo doPico, and Charles E. Reed: A short-term double-blind trial of aerosol triamcinolone acetonide in steroid-dependent patients with severe asthma. Chest 69(4):456-460, 1976.

156. Lal, S., D. M. Harris, K. K. Bhalla, S. N. Singhal, and A. G. Butler: Comparison of beclomethasone dipropionate aerosol and prednisolone in reversible airways obstruction. Brit. Med. J. 3:314-317, 1972.

157. Choo-Kang, Y. F. J., E. Jean Cooper, A. E. Tribe, and I. W. B. Grant: Beclomethasone dipropionate by inhalation in the treatment of airways obstruction. Brit. J. Dis. Chest 66:101-106, 1972.

158. Gaddie, J., I. W. Reid, C. Skinner, G. R. Petrie, D. J. M. Sinclair, and K. N. V. Palmer: Aerosol beclomethasone dipropionate: A dose-response study in chronic bronchial asthma. Lancet 2:280-281, 1973.

159. Smith, A. P., Mollie Booth, and A. J. Davey: Treating asthma. Brit. Med. J. 3:705, 1971.

160. Brown, H. Morrow, G. Storey, W. H. S. George: Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. Brit. Med. J. 1:585-590, 1972.

161. Clark, T. J. H.: Effect of beclomethasone dipropionate delivered by aerosol in patients with asthma. Lancet 1:1361-1364, 1972.

162. Maberly, D. J., G. J. Gibson, and A. G. Butler: Recovery of adrenal function after substitution of beclomethasone dipropionate for oral corticosteroids. Brit. Med. J. 1:778-782, 1973.

163. Brown, H. Morrow, and G. Storey: Beclomethasone dipropionate steroid aerosol in treatment of perennial allergic asthma in children. Brit. Med. J. 3:161-164, 1973.

164. Godfrey, S., and P. König: Beclomethasone aerosol in childhood asthma. Arch. Dis. Childhood 48:665-670, 1973.

165. Dickson, Walter, Catherine E. Hall, Mary Ellis, and Robert H. Horrocks: Beclomethasone dipropionate aerosol in childhood asthma. Arch. Dis. Childhood 48:671-675, 1973.

166. Pines, A.: Beclomethasone dipropionate used as an aerosol in the treatment of asthma. Practitioner 211:86-90, 1973.

167. Graber, Alan L., Robert L. Ney, Wendell E. Nicholson, Donald P. Island, and Grant W. Liddle: Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. J. Clin. Endocrinol. 25:11-16, 1965.

168. Byyny, Richard L.: Withdrawal from glucocorticoid therapy. N. Engl. J. Med. 295:30-32, 1976.

169. Melby, James C.: Systemic corticosteroid therapy: Pharmacology and endocrinologic considerations. Ann. Int. Med. 81:505-512, 1974.