ANNUAL REVIEWS Further
Quick links to online content

Ann. Rev. Pharmacol. Toxicol. 1978. 18:541–61
Copyright © 1978 by Annual Reviews Inc. All rights reserved

PHARMACOLOGICAL CONTROL OF ASTHMA

◆6728

Archie F. Wilson
Departments of Medicine and Physiology, University of California, Irvine, California 92717

Joseph J. McPhillips
Astra Pharmaceutical Products, Inc., Framingham, Massachusetts 01701

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org
by Central College on 12/14/11. For personal use only.

INTRODUCTION

In this review, the terms *asthma, reversible airways obstruction,* and *bronchospasm* are used almost interchangeably. The justification for this approach is the concept, supported by considerable evidence, that asthma represents a final common pathway for many processes that either separately or together produce the clinical syndrome characterized by reversible bronchospasm (1). Additionally, there does not seem to be a generally accepted more specific definition of asthma (2).

Currently, asthma is regarded as a condition resulting from an imbalance of the autonomic nervous system leading to increased airway reactivity. Other processes such as infection or allergy trigger the acute attack (1). The autonomic abnormality may be described as a predominance of α-adrenergic and/or cholinergic activity over β-adrenergic activity in bronchial smooth muscle and, perhaps, bronchial tissue mast cells. Increased α-adrenergic and/or cholinergic activity causes decreased cellular cyclic adenosine monophosphate (cAMP) and/or increased cyclic guanidine monophosphate (cGMP) levels which, in turn, either directly or indirectly (via release of several mediator or bronchoconstrictor substances from mast cells) leads to muscle contraction (bronchospasm). The mediators of muscle contraction include histamine, slow reacting substance of anaphylaxis and others (1). It is thought that, in the presence of increased α-adrenergic or cholinergic activity, infection, allergens, and, in some cases, exercise are more likely to cause mediator release and subsequent bronchospasm. Recently it has been shown that prostaglandins modulate these responses (3).

Because of the multiple factors that interplay in the production of the clinical syndrome of asthma, pharmacological intervention is theoretically possible at any of several processes (Table 1). Pharmacological intervention may take the form of

0362-1642/78/0415-0541$01.00

Table 1 Physiological processes and clinical uses of bronchodilators

Process	Drugs	Clinical use
I. Increase cyclic AMP (and/or decrease cyclic GMP)		
A. β stimulation		
1. Nonspecific	Ephedrine	largely supplanted
	Isoproterenol	largely supplanted
2. Specific β-2	Isoetharine	being supplanted
	Terbutaline	in wide use
	Metaproterenol	in wide use
	Salbutamol	in wide use[a]
	Fenoterol	in wide use[a]
	Carbuterol	investigational
3. Phosphodiesterase inhibition	Theophylline	in wide use
B. α-Adrenergic blockage	Indoramine	investigational
	Thymoxamine	investigational
	Phentolamine	investigational
C. Cholinergic blockage	Atropine	investigational
	Ipratropium	invesitgational
II. Mediator release inhibition	Disodium cromoglycate	prophylaxis only
	Corticosteroids	in wide use
	Immunotherapy (hyposensitization)	in wide use
III. Mediator antagonism		
A. Antihistamines		investigational
B. SRS-A inhibitors	Diethylcarbamazine	investigational
C. Prostaglandins	Prostaglandin E_2	investigational
IV. Antibody formation inhibition	Corticosteroids	in wide use
	Immunosuppressants	investigational
	Immunotherapy ($\downarrow$Ige) (hyposensitization)	in wide use
V. Antigen-antibody interaction interferants	Immunotherapy (blocking antibodies)	in wide use
VI. Modulators (antiinflammatory)	Hydrocortisone	in wide use
	Prednisone	in wide use
	Cloprednol	investigational
	Beclomethasome	in wide use

[a] Investigational in the United States.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

α-adrenergic or cholinergic blockade, β-adrenergic stimulation, phosphodiesterase inhibition (decreased cyclic AMP breakdown), inhibition of mediator release, mediator antagonism, inhibition of antibody formation, interference with antigen-antibody interaction, and modulation of effects of several of the earlier described processes. Hence, many types of antiasthma drugs are available for clinical use and studies are ongoing to evaluate the effectiveness of some of the approaches not yet part of clinical practice. It is also becoming evident that, while specific approaches are useful in some situations in individual patients, in others, these agents may be useless and therapy must be individualized.

DRUGS PRESENTLY USED FOR ASTHMA

Autonomic Agonists and Blockers

ADRENERGIC AGONISTS Sympathomimetic amines have been used for centuries in the pharmacological control of asthma. Although they may differ from one another in several characteristics such as chemical structure, absorption, and metabolism, the fundamental action of these drugs is the same. Each of these agents, when administered in a sufficient dose by an appropriate route, will reduce the work of breathing, relieve symptoms of asthma, and improve ventilation. All of the agents can produce a substantial increase in pulmonary function as a consequence of dilation of the central and peripheral airways brought about by relaxation of airway smooth muscle.

The effect of sympathomimetics on bronchial smooth muscle is mediated by β-adrenergic receptors (4, 5). Available evidence points to the activation of membrane adenylcyclase and enhanced production of cyclic AMP as the mediator of relaxation of smooth muscle (6). The action and mechanism of action of adrenergic agents therefore appear to be identical for all agents in that class. However, each of the drugs has distinguishing features that render some more desirable than others for the pharmacological control of asthma.

Ephedrine and isoproterenol have been available for many years. However, there have been surprisingly few well-controlled studies performed with these drugs until recently when they have been used as comparative drugs in clinical trials designed to evaluate newer bronchodilators.

Ephedrine When used alone, ephedrine is of limited value as a bronchodilator and is only slightly more effective than a placebo in some patients. Several studies have been conducted in which the effect of a single dose of ephedrine on pulmonary function has been evaluated. Average improvement in $FEV_{1.0}$ was 18%. Also, contrary to what is believed, the combination of ephedrine with theophylline did not provide any benefit above that produced by theophylline alone (9). However, the combination did produce a significant increase in the incidence of central nervous system stimulation, insomnia, and gastrointestinal upset.

Although the principal limitations to the use of ephedrine are reported to be tolerance, nervousness, tremor, and tachycardia, the controlled trials did not suggest that any of these are a significant problem (7–9). The principal limitation seems to

be that ephedrine is a weak bronchodilator, the undesirable effects of which are enhanced by combining it with theophylline (9).

Isoproterenol There are studies too numerous to cite which document the efficacy of isoproterenol as a bronchodilator. Administered by inhalation, isoproterenol produces prompt relief of symptoms and measurable increases in $FEV_{1.0}$, airway conductance, and maximal midexpiratory flow rate. At the same time, there are decreases in functional residual capacity and residual volume and airways resistance (10).

Changes in pulmonary function take place quite rapidly following inhalation of isoproterenol; large changes are noted in 30–60 sec (11, 12). The response to therapeutic doses, however, is relatively brief; changes in pulmonary function are usually back to the baseline within 3 hr (11–13), although there are reports of significant effects extending to 5 hr (14).

Isoproterenol is effective only by inhalation or by injection. It is not effective when administered orally because it is metabolized by catechol-O-methyl transferase either in the intestinal wall or during the first pass through the liver following absorption (15). Metabolic studies in humans suggest the intestinal wall as the principal site of metabolism of the oral dose since most of an intravenous dose of isoproterenol is excreted unchanged in the urine (16).

Despite the efficacy of isoproterenol, textbooks, drug compendia, and editorials express concern over the margin of safety of the drug. A high incidence of side effects such as tachycardia, palpitations, and tremor are associated with the use of isoproterenol and there is concern about its potential for aggravating hypoxemia (17). In addition, there is the associated increase in mortality with the use of isoproterenol inhalers by asthmatics (16).

Controlled clinical studies do not consistently reveal problems with isoproterenol when used at therapeutic doses. Occasional episodes of palpitations, tremor, and tachycardia are experienced by some patients but the incidence of such episodes is low when recommended doses are used (11, 13, 14, 19). Higher doses are reported to produce a higher incidence but severity of such episodes was not alarming and not substantially different from these produced by high doses of metaproterenol (20) or salbutamol (21).

Though a causal relationship has not been established, isoproterenol has been implicated as the causative agent in the reported increase in deaths of asthmatic subjects in England and New Zealand during the years 1960 and 1966 (18). The increase in mortality has been attributed to the excessive use of the metered dose inhaler by patients with respiratory difficulty (22). However, the use of a bronchodilator from a metered dose dispenser may be inadequate therapy for a severe, acute attack which requires more intensive and prolonged treatment. The principal danger of inhalers may be an overestimation of their benefit rather than intrinsic toxicity.

β-2 agents The division of β-adrenoceptors into two subgroups designated β-1 and β-2 by Lands and co-workers (5) provided the impetus for the development of

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

agents which were selective
which is mediated by β-2 adrenoceptors (5). Modifications of the isoproterenol molecule have yielded a series of β-2 selective agents such as metaproterenol, salbutamol, terbutaline, fenoterol, and carbuterol.

Designation of compound as a β-2 selective agent is based primarily on data obtained from in vitro studies in which the potency of the compound is established on selected isolated tissues. Most studies have been conducted with isolated guinea pig atrium which serves as the model for β-1 receptor–mediated actions and isolated guinea pig trachea which serves as the model for β-2 receptor-mediated actions.

If one establishes the concentration required to produce equivalent changes in tracheal smooth muscle and cardiac muscle, it is possible to calculate a selectivity index for β-adrenergic agonists based on the ratio of cardiac to tracheal effects.

In a study by O'Donnell & Wanstall (23) in which indices were calculated, metaproterenol had a selectivity index of 3 and terbutaline, 45; isoproterenol had a selectivity index of 0.25 indicating a slight preference for cardiac muscle over tracheal smooth muscle. In a similar study by Malta & Raper (24), metaproterenol had a selectivity index of 6 and terbutaline 64. In a study by Wagner et al (25), salbutamol showed a selectivity index of 250 and terbutaline 138; isoproterenol had a selectivity index of 1.4. Therefore, in vitro studies, in which comparisons are based on equieffective concentrations obtained from dose-response curves, establish that drugs such as salbutamol, terbutaline, and metaproterenol have a relative preference of β-2 receptors with salbutamol being the most selective and metaproterenol the least.

In vivo studies in animals and, in one instance, in humans, have provided results that are consistent with the results of the studies on isolated tissue. Wasserman & Levy (26) compared terbutaline and salbutamol to isoproterenol on the anesthetized dog. Terbutaline and salbutamol were clearly less potent than isoproterenol as cardiac stimulants and bronchodilators. However, there was also a clear separation of the cardiac and pulmonary effects of terbutaline and salbutamol. Similar results were reported by Wagner et al (25) in anesthetized cats.

To the knowledge of the reviewers, there have been only two studies performed in humans in which a sufficient portion of the dose-response curve for changes in pulmonary function and heart rate have been described to establish potency ratios. Figure 1 shows the results of a study by Svedmyr & Thiringer (27) in which a comparison was made of the pulmonary and cardiac effects of intravenous administered salbutamol and isoproterenol on $FEV_{1.0}$ and heart rate. In fact, the changes in $FEV_{1.0}$ reached an asymptote while heart rate continued to increase as the infusion rate increased. The lower part of the figure depicts the response to salbutamol. There is a clear separation of the dose-response curves with changes in $FEV_{1.0}$ occurring at lower doses than changes in heart rate. Comparisons of equieffective doses yield a selectivity index of approximately 8. A similar study conducted with terbutaline by the same authors (28) showed a similar separation of cardiac and pulmonary effects. Under the same conditions, terbutaline had a selectivity index of 5. In both instances, the selectivity for the respiratory tract is considerably less than was observed in vitro or in animals. The reduction in selectivity of

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

these agents when administered to humans may be the result of reflex cardioacceleration combined with a direct effect of the drugs on the heart. Sackner et al (29) studied the cardiovascular effects of terbutaline in normal subjects following subcutaneous administration. They observed an increase in cardiac output, heart rate, stroke volume, and calf blood flow. The increased cardiac output associated with decreased vascular resistance is consistent with reflex cardioacceleration. It is important to understand that these agents are relatively selective and that they are not devoid of cardiovascular effects.

The important question to be answered about β-2 agents is whether they offer an advantage over currently available drugs for the treatment of asthma.

The limited data available in humans suggest that terbutaline and salbutamol have less potential for cardiac stimulation than isoproterenol when administered parenterally (27, 28) or by inhalation (29–31) and therefore probably have a greater margin of safety than isoproterenol.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

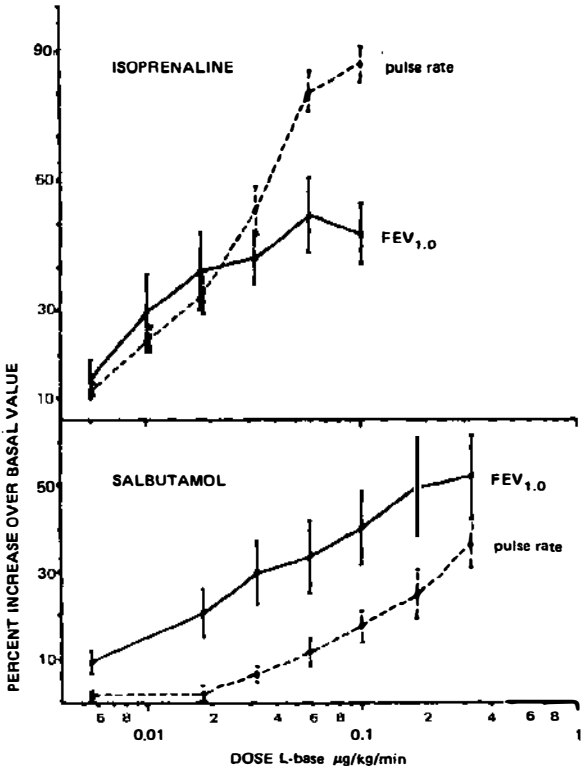

Figure 1 Mean dose-response curves for bronchodilator and cardiostimulatory effects of isoproterenol (isoprenaline) and salbutamol. From (27), with permission.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Another advantage of these agents, which is unrelated to β-2 selectivity, is effectiveness following oral administration, a property also not shared with isoproterenol. Substitution of the one of the phenolic hydroxyl groups or placing the phenolic hydroxyl groups in the 3–5 position yields compounds which are not metabolized by catechol-O-methyl transferase. Isoproterenol, when administered orally, is inactivated either in the intestinal wall or during the first liver following absorption (15). The advantage of β-2 agents, therefore, is that they are effective bronchodilators which have less potential for cardiac stimulation than isoproterenol and which are effective when administered orally. Since tremor of skeletal muscle is mediated by β-2 adrenoceptors, this side effect may be a limiting side effect of these agents (32).

Tolerance There is concern about acquired tolerance to the bronchodilator action of sympathomimetic drugs because of possible development of reduced effect of endogenous mediators. Hence, prolonged use of a drug that initially produced relief of symptoms might produce gradual deterioration. Acquired tolerance to the bronchodilator action of ephedrine was reported by Herxheimer in 1948. He observed a rapid decline in the response to high doses of ephedrine (33). However, subsequent studies with various sympathomimetic agents, including salbutamol (37), metaproterenol (38), terbutaline (36), and even ephedrine in lower, but currently recommended, doses have failed to corroborate his results (34–36).

Contradictory results with terbutaline have been reported by Jenne and co-workers (39). This group has criticized studies in which patients were permitted use of sympathomimetics until the evening prior to the start of the study. This situation appears to exist in most investigations and may have produced tolerance prior to entry into a study. The interpretation of results is complicated by the observation that, in the study of Jenne (39) as well as a year-long study (36), improvement of the baseline pulmonary function parameters occurred. It is also clear that if tolerance does develop, it is not progressive at recommended doses.

In all of the studies cited above, the presence or absence of tolerance has been decided on the basis of the response to single-dose challenges. Judgments about changes in sensitivity to a drug are better made upon shifts in the position of dose-response curves; this is especially critical when changes in sensitivity are small (40). Svedmyr and co-workers (41) administered terbutaline to a group of asthmatics for one year. None of the subjects had received any drugs prior to entry into the study so there was no question of prior existence of tolerance. At intervals of 1, 2, 3, 6, 9, and 12 months, complete dose-response curves for intravenously administered isoproterenol were obtained for changes in pulmonary function, heart rate, and tremor activity. While they did observe a shift in the dose-response curve for heart rate, there was no evidence of acquired tolerance to the pulmonary effect of isoproterenol nor was there any deterioration of lung function; in fact, baseline values improved over the 12-month period. A similar approach was used by Holgate & Tattersfield (42) to investigate the effects of chronic administration of salbutamol on pulmonary function in normal subjects. They measured dose-related changes in specific airway conductance and found that the dose-response curves shifted repre-

senting a lessened response as daily salbutamol dosages were increased. An additional interesting observation was restoration of normal sensitivity following intravenous hydrocortisone.

It appears that the issue of tolerance will not be easily resolved. If tolerance does develop, the data from controlled clinical studies indicate that it is probably not a clinical problem and does not appear to severely compromise therapy.

α-ADRENOCEPTOR BLOCKING AGENTS Several reports have appeared recently which suggest that α-adrenergic blocking agents may be of some value in the control of asthma. The beneficial effect of α-adrenergic blockade is predicated on involvement of α-adrenoceptors in bronchoconstriction (43). Administration of α-adrenoceptor blocking agents has been shown to be moderately effective in producing bronchodilation in asthmatics (44). Thymoxamine, an α-blocker, was administered to ten asthmatic subjects by inhalation and produced a 45% increase in specific airway conductance. Although the response to thymoxamine was greater than the response to inhaled saline, it was significantly less than the response to inhaled isoproterenol. Thymoxamine also inhibited exercise-induced bronchospasm in 12 of 13 subjects and was as effective as disodium cromoglycate (45). Thymoxamine does not appear to be a very potent drug for treatment of bronchospasm, and it has a duration of action of approximately 60 min. In addition, the drug is reported to be irritating when inhaled (44). The value of this agent is yet to be established.

ACETYLCHOLINE BLOCKERS The maintenance of a mild degree of airway tone in animals and man is mediated by parasympathetic cholinergic nerves (46, 47). Furthermore, inhalation of irritants will provoke bronchoconstriction in asthmatics which can be prevented by the prior administration of atropine (48).

Systemic administration of atropine is not an acceptable treatment for asthma because side effects such as mydriasis, cycloplegia, xerostomia, and urinary retention are unavoidable. Administration of anticholinergics by inhalation, however, may be a practical alternative route since undesirable effects are much rarer. At least part of the chronic airway obstruction in many perennially asthmatic children is a consequence of parasympathetically mediated bronchospasm (49). Administration of atropine by inhalation did not produce mydriasis, cycloplegia, or tachycardia. The author correctly points out that despite the efficacy of inhaled atropine in the acute situation, the value of chronically administered atropine has yet to be evaluated.

An atropine derivative, N-isopropyl nortropine methyl bromide or ipratropium bromide, has been investigated as a potential bronchodilator when administered by inhalation from a pressurized metered dose dispenser. The results of clinical studies conducted on patients with chronic lung disease show the drug to be effective (50–52). The drug appears to have a high order of potency. Results of a dose-response study by Gross (53) provide evidence of an effect on pulmonary function at a dose of 10 μg. Higher doses were not more effective but may have produced a slightly longer duration of action. Since ipratropium bromide and atropine had a greater effect on maximal midexpiratory flow rate than on $FEV_{1.0}$ (49, 53) these agents may have a preferential action upon peripheral airways.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Phosphodiesterase Inhibitors

Theophylline has been used in the management of asthma since 1937 when Herrmann & Aynesworth (54) reported on the successful treatment of status asthmaticus with intravenous theophylline ethylenediamine (aminophylline) in 16 patients. The action of theophylline in asthma is a consequence of relaxation of bronchial smooth muscle attributable to the inhibitory action of theophylline on phosphodiesterase, an enzyme that modulates the intracellular concentration of cyclic AMP. Inhibition of phosphodiesterase and the subsequent accumulation of cyclic AMP leads to relaxation of bronchial smooth muscle and relief of obstruction (6, 55).

The most significant recent advance in the control of asthma with theophylline has been the development of sensitive methods to measure plasma theophylline concentrations. The ability to monitor the concentration of theophylline in blood has permitted the study of the pharmacokinetics of theophylline (56) and consequently the ability to design optimal dose regimens for asthmatic patients (57, 58). An accurate and specific assay for plasma theophylline has been reported by Thompson et al (57) and by Sitar et al (59). The methods employ high pressure liquid chromatography which permits measurement of serum theophylline levels using small volumes of blood without interference from caffeine, theobromine, or theophylline metabolites. In addition, Levy et al (60) have reported a method by which plasma levels can be estimated by assaying the concentration of theophylline in saliva, thereby providing a noninvasive and painless method for routine monitoring of blood levels.

The relationship between the plasma concentration of theophylline, improvement in pulmonary function, and toxicity has been assessed by several investigators with reasonable agreement in the results (58, 61, 62). The optimal concentration appears to be between 10 and 20 μg/ml. Levels of theophylline within this range provide substantial improvements in pulmonary function with minimal toxicity.

Improvement in pulmonary function is minimal with plasma concentration between 5 and 10 μg/ml. However, Maselli et al (63) reported increases in $FEV_{1.0}$ of 60% in children 4 to 15 years with plasma levels of 6 to 8 μg/ml.

Ruffin et al reported wide variation in the dose of theophylline required to produce optimal blood levels (56). Oral doses of terbutaline required to produce optimal blood levels varied between 400 and 3200 mg over a 24-hr period. The reason for the variation is apparently the result of wide variation in the rate of metabolism of theophylline. In 10 patients in whom the dispostion of theophylline was measured, the half-life varied between 181 and 571 min. The average half-life for the group was 348.4 min $\pm$ a standard deviation of 119.7 min. The coefficient of variation was 34%. Children may metabolize theophylline more rapidly since Maselli et al (63) reported an average half-life of 3.6 hr (216 min) in children aged 5–15 years.

The manifestations of theophylline toxicity in order of frequency are irritability, dehydration, severe vomiting, hematemesis, stupor, and convulsions (64). Piafsky & Ogilvie (61) report nausea and vomiting as the most frequent and earliest side effects with chronic oral therapy, which suggests an irritant effect on the gastrointestinal tract. However, an interesting finding in the study by Jenne et al (56) was the

absence of nausea at plasma levels below 13 μg/ml suggesting that nausea is not the result of a direct irritant effect of theophylline on the gastrointestinal mucosa but rather perhaps a consequence of stimulation of the vomiting center in the brain. According to Piafsky & Ogilvie, 5–15% of patients may not tolerate oral theophylline even when plasma levels are less than optimal, and a local irritant effect in the gastrointestinal tract may be predominant in those patients (61).

Though toxicity of theophylline is most prevalent following intravenous administration, this is a relatively safe route of administration if the dose and rate of administration are correct. For example, Maselli et al (63) administered 4 mg/kg intravenously over a period of 4 to 5 min and produced dramatic improvements in pulmonary function with no side effects. Maximal theophylline levels were 8 μg/ml. As with most drugs, attention to the factors that can affect the dose will reduce problems to a minimum.

Mast Cell Stabilizers

Disodium cromoglycate (DSC) is a unique drug that has no bronchodilator properties; DSC rather prevents bronchospasm probably by stabilizing mast cells so that release of performed mediators by antigen-antibody reaction or other stimuli is inhibited (65). Hence, DSC is probably more effective in those instances in which mediator release is a central problem, such as allergy; it is much less useful in infectious asthma (asthmatic bronchitis) (66). Although the likelihood of DSC preventing bronchospasm in a given patient is difficult to predict, certain generalizations are possible. DSC therapy is unlikely to be successful in patients who have perennial or continual asthma and in patients who wheeze only during attacks of bronchitis. DSC is more likely to be successful in patients who have a clear-cut causality.

DSC is a highly insoluble powder which must be inhaled directly into the lung to be effective. It is mixed with lactose, packaged into a gelatin capsule, and placed within a special device for inhalation called a Spinhaler® (67). The Spinhaler allows the capsule to be punctured and the powder to be inhaled utilizing the patients' own inspiratory airflow (67). For optimal results it is necessary for the patient to be relatively unobstructed because (*a*) deep bronchial deposition depends upon good airflows, (*b*) the powder may be irritating and actually cause temporary bronchospasm, and (*c*) DSC is not a bronchodilator and is for prophylactic use only.

One of the great advantages of DSC is that, other than in a few instances, it is virtually free of side effects or toxicity (61). Because DSC is not a bronchodilator, it has not always been easy to prove its effectiveness in chronic asthma and, frequently, patients' diaries or reduction in usage of other medication have been the only manifestations of its effectiveness (2). DSC should be given for a few weeks before a decision is made that it is not effective. Because some patients respond dramatically to DSC, other medications are often decreased or stopped. When corticosteroids are sharply reduced or discontinued, symptoms of steroid lack may appear including rheumatic complaints, lack of energy, hypotension, and Addisonian crisis (61). Therefore, if the patient has received corticosteroids for more than a few weeks, they should be slowly tapered to allow time for return of endogenous adrenal function.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Mediator Inhibitors

ANTIHISTAMINICS Even though histamine has been repeatedly identified as a prominent constituent of mast cells and is released in large quantities following antigen-antibody interaction (68), histamine is thought to be of relatively little importance in clinical asthma, presumably because of the importance and presence of other mediators (69). However, recently several investigators have reported some beneficial effects with doses of antihistaminics higher than those used for allergic rhinitis (69–71); these effects were particularly noticeable when the antihistamine was given intravenously (70). One interesting study reported antihistamine inhibition of the immediate but not the delayed asthmatic response (3–13 hr) to allergen; corticosteroids blocked the late but not immediate response, while disodium cromoglycate blocked both responses (71). It should also be pointed out that antihistamines do not prevent histamine release but rather antagonize histamine-induced tissue damage (68). Hence, antihistamines might be expected to be most effective when administered prior to, for example, allergen inhalation, since they do not inhibit the late of delayed asthmatic response which apparently is due to other mediators. These agents deserve further study.

SRS-A INHIBITION Diethylcarbamazine is able to antagonize the release of slow-reacting substance of anaphylaxis (SRS-A) from mast cells. In general, diethylcarbamazine has not been found to be useful in the treatment of clinical asthma (72,73). However, this agent was shown to probably benefit exercise-induced asthma in children in one study (72). These results do not seem very encouraging for future use of, at least, this agent.

PROSTAGLANDINS Though prostaglandins (PG) are not mediator inhibitors, both the bronchoconstrictor $F_2\alpha$ ($PGF_2\alpha$), and the bronchodilator, E (PGE_2) are released from lung by allergic, chemical, and physical stimuli (74, 75). It was therefore hoped that PGE_2 might be a useful bronchodilator. Unfortunately, this agent is irritating when inhaled and is apparently rapidly destroyed prior to reaching the appropriate sites when administered intravenously (76). While inhaled PGE_2 does block bronchospasm produced by several modalities, it is not more effective than other, nonirritating substances (76–78).

Glucocorticoids

Glucocorticoids are probably the most reliably effective agents which may be used for treatment of asthma. If glucocorticoids were free of side effects, there would be little need for other antiasthma drugs. Of course, chronic glucocorticoid administration produces a dose- and time-dependent suppression of endogenous adrenal cortical function as well as manifestation of corticoid overstimulation: osteoporosis, glucose intolerance, activation of latent infection, delayed healing, etc.

Glucocorticoids have at least two actions: reduction of inflammation from any cause and potentiation of β-agonist activity (79, 80). When given acutely they produce beneficial effects within 1 to 12 hr (79–81). Glucocorticoids are available in two major forms: systemic, which includes oral and intravenous, and inhaled. Systemic administration is discussed first.

Systemic steroids are utilized in treatment of severe acute and chronic asthma which does not respond to other agents. Because of the multiplicity of side effects, they should never be used as first-line agents. The usual choice for status is 100–200 mg of intravenous hydrocortisone given every 2–6 hr (82). The usual choice for severe chronic asthma is oral prednisone or prednisone utilized in the smallest effective dose, preferably given once every other day. The latter drugs and procedure are utilized to minimize adrenal suppression since, among the currently available glucocorticoids, these two agents have relatively short half-lives (about 6 hr) (83). A new agent, cloprednol, which has a shorter half-life, may be given once daily without adrenal suppression (84).

After several weeks of daily administration of hydrocortisone and/or prednisone, adrenal suppression is likely and steriod withdrawal must be approached with caution. Acute withdrawal of steroids may produce a variety of otherwise obscure rheumatic and other complaints and even hypotension. In particular, stressful situations such as surgery or acute illness will usually require temporary steroid administration. This situation may persist for six months or more (85).

Because glucocorticoids are metabolized by hepatic microsomes, concurrent administration of phenobarbital, a component of some bronchodilator formulations, will increase steroid turnover and reduce the effectiveness of any given dose (86). Additionally, free blood cortisol may be less than expected after hydrocortisone injection in patients chronically treated with glucocorticoids (87).

One of the most exciting advances in the treatment of chronic asthma has been the introduction of the surface-active inhaled steroid, beclomethasone (88, 89). This agent has excellent topical activity and, in daily doses of 800 μg or less, has no systemic effects (88, 89). In general, patients requiring up to 20–25 μg prednisone daily may receive relief from inhaled beclomethasone with almost no side effects (except for oral moniliasis, which is usually clinically inapparent and insignificant). The previously mentioned cautions about rapid removal of chronically administered oral glucocorticoids must also be followed. Another withdrawal (from oral steroids) symptom observed is appearance of previously suppressed symptoms of allergic rhinitis. Because beclomethasone does not have an immediate effect and because it is inhaled from a pressurized cannister, it should not be relied upon to treat acute exacerbations of asthma; other agents and preparations are more appropriate for treatment of the acutely ill patient.

The glucocorticoids, betamethasone and dexamethasone, have been also utilized by inhalation; dexamethasone has less topical systemic separation of activity than beclomethasone and betamethasone and therefore is inferior for the treatment of asthma (90).

MODES OF ADMINISTRATION

Inhaled

The object of all pharmacological therapy is to deliver the minimum amount of drug necessary to effect the desired action in the appropriate anatomic site; by this means undesired drug effects in other organs are usually avoided. In the specific instance of asthma, the desired site is the airways and inhalation of bronchodilators is, at least

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

theoretically, the preferred method in uncomplicated situations. However, inhalation is ineffective with certain types of drugs such as theophylline (91), and in certain situations, e.g. severe obstruction (92); in addition, inhalation may be inconvenient in patients requiring chronic therapy; finally, inhalation is the only effective means of administration of disodium cromoglycate and beclomethasone. In general, while almost every possible means of administration of drugs is available—oral, intravenous, rectal, subcutaneous, as well as inhaled solid and liquid aerosols—usually only one or two of these types of preparations are desirable for specific applications.

For inhaled pharmaceutical aerosols to effectively deposit in diseased airways, the particles should probably be about 1–7 μm in size; electric charge and hygroscopicity introduce further uncertainty (93). Small particles preferentially penetrate deep into the lung thereby depositing in smaller airways, while large particles preferentially deposit in large airways. Since asthma may involve large and/or small airways (1), a range of particles may be advisable; this problem is under active investigation. The particle size produced by metered dose cannisters pressurized with propellant is predictable at the nozzle since the active ingredients are dry and have been previously sized (usually 3–5 μm). However, since the dry particles are hygroscopic, they probably grow somewhat within the airways, thereby affecting deposition.

Patients are usually instructed to exhale maximally and activate the cannister as they breathe in thereby (presumably) carrying the particles deep into the lung. The patient is instructed to pause at full inspiration for a few seconds, to allow for maximum particle settling, then to exhale slowly. While it has been the common practice to activate the cannister early in inspiration, it has recently been reported that greater bronchodilation occurs when the cannister is activated later in inspiration, presumably because airways are larger at larger lung volumes (94). Another factor controlling aerosol deposition in airways is the inertia imparted to the drug particles by the force of the propellant. If this inertia is greater than the effect of bulk airflow upon particles, the aerosol will impact and deposit upon the posterior pharyngeal wall. Several techniques to reduce this phenomenon have been devised: One is to activate the cannister during inhalation with an open mouth, which reduces the initial particle velocity by mixture with a larger, slower moving airstream; the other is to extend the distance between the outlet nozzle and the mouth, allowing a greater distance for the high initial particle velocity to be dissipated.

Aerosols produced by both pressurized cannisters and wet liquid nebulizers should be directed to airways which are ventilated. Therefore, well-ventilated portions of the lung should receive a large proportion of inhaled aerosol and poorly ventilated regions, which are in greater need of medication, should receive the least amount of active drug. However, investigation of this problem in patients with bronchitis and asthma demonstrated only a rough nonsignificant correlation between regional distribution of ventilation and aerosol deposition (95). Yet, an effect, consistent with this hypothesis, is seen in patients with greater degrees of bronchospasm (92). Inhalation of dry particles via pressurized cannisters is usually preferable to liquid particles generated by aerosol devices because the dry particle size is much better controlled so that there is little or no deposition within the generation apparatus. Hence only one tenth to one twentieth of the amount needed with liquid

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

nebulizers need be used (96). However, in severely obstructed patients, liquid particles tend to be more effective, presumably because of the use of positive pressure apparatus (IPPB) for aerosol generation and delivery (92).

Systemic

Drugs may enter the bloodstream by absorption from the gastrointestinal tract after oral administration, from skin or muscle depots following injection, or, of course, by direct infusion. Almost every drug discussed above has been given intravenously. The intravenous route has the advantages of complete absorption and immediate delivery. However, because of inconvenience and impracticality of repeated intravenous injections, this route can be justified only for severely ill patients. Intravenous hydrocortisone and aminophylline are frequently used in status asthmaticus (11). Intravenous autonomic agents are still investigational; they seem to offer little advantage over standard treatment (11).

Subcutaneous administration of epinephrine and terbutaline has been extensively studied (29). Subcutaneous injection provides a good combination of immediate and somewhat sustained activity for patients with acute asthma; usually it is utilized as initial therapy (to be followed if necessary by intravenous aminophylline) (83).

Disodium cromoglycate is not absorbed from the gastrointestinal tract and therefore is active only by inhalation (65). Isoproterenol is inactivated in the gastrointestinal tract and liver and can therefore be used only by inhalation or injection (15, 16). Theophylline preparations are poorly absorbed in the presence of food and therefore should be administered prior to meals (51).

BRONCHODILATORS AND ARTERIAL OXYGEN

The action of bronchodilators on blood gases, particularly arterial oxygen tension, is not well understood. There is a direct relationship between arterial oxygen tension and pulmonary function expressed as a percentage of the predicted $FEV_{1.0}$ value (97). From this relationship an increase in arterial oxygen would be anticipated following administration of a bronchodilator which produced improvement in pulmonary function. However, bronchodilators do not appear to affect the arterial oxygen tension of patients with obstructive lung disease, and that is illustrated by the results of studies that are summarized in Table 2. With the exception of the response to isoproterenol reported by Knudson & Constantine (98), which was an average decrease of 8 mm Hg, average changes were very slight and of no clinical significance. In many studies, improvement in pulmonary function in some patients was associated with a substantial decrease in PaO_2 following treatment with bronchodilators (97, 106, 107). The failure of arterial oxygenation to improve would be surprising if account were not taken of changes in ventilation:perfusion relationships especially when bronchodilators are inhaled. Episodes of aggravated hypoxemia are not restricted to isoproterenol (97); theophylline (107) and β-2 selective agents which were thought not to cause aggravation of hypoxemia have also been found to precipitate such episodes (103, 105). The phenomenon does not appear to be limited only to bronchodilators administered by inhalation because episodes have been reported following intravenous and subcutaneous administration.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Table 2 Arterial oxygen tension in humans before and after administration of bronchodilators

Bronchodilator	Route of administration	Arterial oxygen tension		Reference
		Before	After	
Isoproterenol	inhalation	78.2	64.1	98
Isoproterenol	inhalation	75.2	71.9	99
Salbutamol	inhalation	73.9	76.0	100
Salbutamol	oral	73.8	76.8	101
Salbutamol	intravenous	69.0	74.0	102
Terbutaline	inhalation	70.7	69.4	103
Terbutaline	oral	73.4	75.3	101
Terbutaline	subcutaneous	64.4	66.7	104
Rimiterol	inhalation	71.2	70.3	105

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Chick and co-workers (108) studied the response of a group of asthmatics to inhaled isoproterenol and were able to divide the group into seven subjects in whom there was a decrease in PaO_2 and nine subjects in whom PaO_2 did not change. The two groups could not be distinguished on the basis of spirometry. However, by using a nitrogen washout technique, they were able to measure the volume, the ventilation, and the perfusion of poorly ventilated alveoli. Those subjects who responded to isoproterenol with a decrease in PaO_2 had a greater volume of poorly ventilated alveoli which were also more ventilated than subjects in whom PaO_2 did not change. Moreover, in those subjects who responded with a decrease in PaO_2, isoproterenol caused an increase in the perfusion of poorly ventilated alveoli, whereas in those subjects in whom there was no change in PaO_2, perfusion of poorly ventilated alveoli was decreased by isoproterenol.

Hales & Kazemi (109) have suggested that the increase of poorly ventilated alveoli is related to attenuation of the pulmonary vasoconstrictor response which is triggered by alveolar hypoxia. They point out that one of the primary adjustments for ventilation-perfusion imbalance is the ability of the pulmonary vasculature to constrict and to shift perfusion away from poorly ventilated lung zones where PaO_2 is low. Their experiments in dogs revealed that administration of aminophylline and epinephrine attenuates the vasoconstrictor response to hypoxia.

DRUGS OF CHOICE IN CLINICAL SITUATIONS

It is clear from the preceding discussion that there are many treatment possibilities for individual asthmatic patients; choice includes not only drugs but also route of administration. The clinical presentation of the types of asthma, which may be characterized as intermittent, perennial, or exercise-induced, will be separately considered. While it is also true that the clinical picture may change with time in individual patients, this classification is a useful approach for, at least, discussion purposes.

Intermittent Asthma

The patient who suffers mild acute intermittent bronchospasm often after exposure to allergen or during an attack of bronchitis will usually respond to many of the drugs listed in Table 1. If the attack is likely to be limited, because of removal of the offending allergen, etc, use of metered dose inhalation of a specific β-2 agonist aerosol or subcutaneous injection of epinephrine is suggested. If the attack does not quickly and completely respond to these measures, oral therapy with a β-2 agonist or theophylline is probably indicated. Failure to respond to oral therapy requires additional measures described below under therapy for status.

Perennial Asthma

The treatment of perennial or chronic asthma requires not only knowledge of pharmacology but also considerable patience on the part of the physician. It is useful to consider the therapeutic possibilities in three phases.

The first phase of treatment of chronic asthma is oral therapy with a β-2 agonist or theophylline. While it is popular for physicians to prescribe both of these types of drugs together, the available evidence suggests that increased toxicity, not therapeutic response, will be the result (9). It has been shown that continuous administration of β-2 agonist is associated with gradual improvement of baseline pulmonary function without any decrease in peak response to individual doses of medication (36), suggesting that therapy for chronic asthma should be continuous and not be decreased when symptoms abate slightly. Utilization of an inhaled adenergic agent as the major or sole treatment for chronic asthma is theoretically possible but has not been put to critical test.

The second phase of treatment of chronic asthma is utilization of either or both of the inhaled drugs, disodium cromoglycate and beclomethasone. As was pointed out earlier, these drugs are primarily prophylactic and much more effective when inhaled into relatively unobstructed airways. Because of the latter consideration, other, usually oral drugs, should not be discontinued, at least until the patient is relatively asymptomatic. Some clinicians prefer to use either of these agents as the first phase of treatment of chronic asthma, particularly if the condition is mild.

Oral corticosteroids constitute the third phase of treatment of chronic asthma. While these agents may be utilized with usually tolerable side effects for periods of a few weeks, longer usage is more likely to be associated with undesirable results. Therefore, continuous administration of glucocorticoids is only undertaken when the agents used in phases one and two are relatively ineffective. Most clinicians believe that it is not necessary to achieve completely normal pulmonary function, rather only an acceptable degree of physical activity.

Side effects may be minimized by use of relatively short acting agents (prednisone, prednisolone, and cloprednol) administered once daily or, preferably, once every other day. Particular care to evaluate the possibilities of activation of latent tuberculosis and diabetes, bleeding or performation of duodenal or gastric ulcers, and development of osterporosis and Cushing's syndrome should be undertaken.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Status Asthmaticus

Status is considered as severe asthma, usually developing or worsening acutely, which does not respond to the medication which is usually used by the patient for asthmatic attacks. Since status can rapidly progress to respiratory failure and potential death, status must be treated vigorously and rapidly. In patients who have not received large amounts of adrenergic agonists within the previous few hours, subcutaneous or inhaled adrenergic agonists may be initially given. If there is no response, the patient should be hospitalized and given intravenous hydrocortisone and aminophylline. Some physicians prefer not to utilize adrenergic agonists. Other measures include use of oxygen, fluids, and ventilators as appropriate (82).

To prevent recurrence and ensure continued improvement, oral medications, including adrenergic agonists or theophylline and, probably, glucocorticoids, should be prescribed after the acute problem has subsided. If glucocorticoids are prescribed, they may usually be tapered and discontinued rapidly (82).

Exercise-Induced Asthma

In many, particularly young, asthmatics, exercise will induce an acute, brief attack of asthma about 6–8 min following the exercise. In some patients, this is the only manifestation of their disease. This condition may be treated after it has occurred but is best prevented by prior administration of drugs. In one study in which a number of drugs were evaluated in the same group of patients, salbutamol was universally effective and theophylline and disodium cromoglycate were 80% and 60% effective (110); previously, this group had shown that antihistamines and steroids were ineffective (111).

Literature Cited

1. Wilson, A. F., Galant, S. P. 1974. Recent advances in the pathophysiology of asthma. *West. J. Med.* 120:463–70
2. Porter, R., Birch, J., eds. 1971. *Identification of Asthma,* p. 174. Edinburgh & London: Churchill-Livingstone. 179 pp.
3. Pasargiklian, M., Bianco, S., Allegra, L. 1976. In *Advances in Prostaglandin and Thromboxane Research,* ed. B. Samuelsson, R. Paoletti, 1:461–75. New York: Raven. 596 pp.
4. Alquist, R. P. 1948. A study of adrenotropic receptors. *Am. J. Physiol.* 153: 586–600
5. Lands, A. M., Arnold, H., McAuliff, J. P., Luduena, F. P., Brown, T. G. Jr. 1967. Differentiation of receptor systems activated by sympathomimetic amines. *Nature* 214:597–98
6. Schultz, G., Hardman, J., Sutherland, E. W. 1973. In *Asthma, Physiology, Immunopharmacology and Treatment,* ed. K. F. Austen, L. M. Lichtenstein, pp. 123–38. New York: Academic. 323 pp.
7. Dulfano, M. J., Glass, P. 1973. Evaluation of a new B_2-adrenergic receptor stimulant, terbutaline, in bronchial asthma. II. Oral comparison with ephedrine. *Curr. Ther. Res. Clin. Exp.* 4: 150–57
8. Gumei, A., Miller, W. F., Paez, P. N., Gast, L. R. 1975. Evaluation of a new bronchodilator, terbutaline. *Pharmacology* 13:201–11
9. Weinberger, M., Bronsky, E. 1975. Interaction of ephedrine and theophylline. *Clin. Pharmacol. Ther.* 17:585–92
10. McFadden, E. R. Jr., Kiser, R., de Groot, W. J. 1973. Acute bronchial asthma. Relations between clinical and physiologic manifestations. *N. Engl. J. Med.* 288:221–25
11. Roth, M. J., Wilson, A. F., Novey, H. S. 1977. A comparative study of the aerosolized bronchodilators, isoproterenol, metaproterenol and terbutaline in asthma. *Ann. Allergy* 38:16–21
12. Sobol, B., Reed, A. 1974. The rapidity of onset of bronchodilation. A compari-

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

son of alupent and isoproterenol. *Ann. Allergy* 32:137–41
13. Segal, M. S., Ishikawa, S. 1975. Isoproterenol aerosols. *Ann. Allergy* 34: 205–9
14. Huhti, E. 1972. Clinical comparison of terbutaline and isoprenaline administered by inhalation. *Ann. Clin. Res.* 4:152–64
15. Conolly, M. E., Davies, D. S., Dollery, C. T., Morgan, C. D., Patterson, J. W., Sandler, M. 1972. Metabolism of isoprenaline in dog and man. *Br. J. Pharmacol.* 46:558–72
16. Davies, D. S. 1972. Metabolism of isoprenaline and other bronchodilator drugs in man and dog. *Bull. Physio-Pathol. Respir.* 8:679–82
17. Flenley, D. C. 1975. In *New Directions in Asthma,* ed. M. Stein, 30:495–522. Park Ridge, Ill.: Am. Coll. Chest physicians
18. Speizer, F. E., Doll, R., Heaf, P. 1968. Observations on recent increases in mortality from asthma. *Br. Med. J.* 1:335–39
19. Shih, C., Williams, M. H. Jr. 1975. Cardiac response to repeated doses of isoproterenol aerosol. *Ann. Intern. Med.* 83:208–11
20. Holme , T. H. 1968. A comparative clinical trial of metaproterenol and isoproterenol as bronchodilator aerosols. *Clin. Pharmacol. Ther.* 9:615–24
21. Spector, S., Gomez, M. 1977. Do e response effects of albuterol aerosol compared with isoproterenol and placebo aerosols. *J. Allergy Clin. Immunol.* 59:280–86
22. Speizer, F. E., Doll, R., Heaf, P., Strang, L. B. 1968. Investigations into use of drugs preceding death from asthma. *Br. Med. J.* 1:339–43
23. O'Donnell, S. F., Wanstall, J. C. 1974. Potency and selectivity *in vitro* of compounds related to isoprenaline and orciprenaline on beta-adrenoceptors in the guinea pig. *Br. J. Pharmacol.* 52:407–17
24. Malta, E., Raper, C. 1974. Non-catechol phenylethanolamines; agonistic and antagonistic actions on beta adrenoceptors in isolated tissues from the guinea pig. *Clin. Exp. Pharmacol. Physiol.* 1:259–68
25. Wagner, J., Reinhardt, D., Schumann, H. J. 1973. Comparison of the bronchodilator actions of i oprenaline Th 1165a, terbutaline and salbutamol in cats and isolated organ preparations. *Res. Exp. Med.* 162:49–62
26. Wasserman, M. A., Levy, B. 1974. Cardiovascular and bronchomotor responses to selective beta adrenergic receptor agonists in the anesthetized dog. *J. Pharmacol. Exp. Ther.* 189: 445–55
27. Svedmyr, N., Thiringer, G. 1971. The effects of salbutamol and isoprenaline on beta-receptors in patients with chronic lung disease. *Postgrad. Med. J. Suppl.* 47:44–46
28. Thiringer, G., Svedmyr, N. 1976. Comparison of infused and inhaled terbutaline in patients with asthma. *Scand. J. Respir. Dis.* 57:17–24
29. Sackner, M. A., Daugherty, R., Watson, H., Wanner, A. 1975. Hemodynamic effects of epinephrine and terbutaline in normal man. *Chest* 68:616–733
30. Lahdensvo, A., Alanko, K. 1976. The efficacy, as modified by the circadian rhythm, of salbutamol administered by routes. *Scand. J. Respir. Dis.* 57:231–38
31. Bachus, B. F., Sherter, C. B., Snider, G. L. 1976. Bronchodilator effect of terbutaline aerosol in reversible airways disease. *Am. Rev. Respir. Dis.* 113:161
32. Thiringer, G., Svedmyr, N. 1975. Evaluation of skeletal muscle tremor due to bronchodilator agents. *Scand. J. Respir. Dis.* 56:93–102
33. Herxheimer, H. 1946. Dosage of ephedrine in bronchial asthma and emphysema. *Br. Med. J.* 2:350–52
34. Taylor, W. F., Heimlich, E. M., Strick, L., Busser, R. 1965. Ephedrine and theophylline in asthmatic children: Quantitative observation on the combination and ephedrine tachyphylaxis. *Ann. Allergy* 23:437–40
35. May, C. S., Pickup, M. E., Patterson, J. W. 1975. The acute and chronic bronchodilator effects of ephedrine in asthmatic patients. *Br. J. Clin. Pharmacol.* 2:533–37
36. Wilson, A. F., Novey, H. S., Cloninger, P., Davis, J., White, D. 1976. Cardiopulmonary effects of long term bronchodilator administration. *J. Allergy Clin. Immunol.* 58:204–12
37. Sims, B. A. 1974. Investigation of salbutamol tolerance. *Br. J. Clin. Pharmacol.* 1:291–94
38. Sackner, M. A., Silva, G., Zucker, C., Marks, M. 1977. Long term effect of metaproterenol in asthmatic children. *Am. Rev. Respir. Dis.* 115:945–53
39. Jenne, J. W., Chick, T. W., Strickland, R. D., Wall, F. J. 1977. Subsensitivity of beta responses during therapy with long

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

acting beta 2 preparation. *J. Allergy Clin. Immunol.* 59:383–90
40. Trendelenburg, U. 1963. Supersensitivity and subsensitivity to sympathomimetic amines. *Pharmacol. Rev.* 15:225–76
41. Svedmyr, N. L., Larsson, S. A., Theringer, G. K. 1976. Development of "resistance" in beta adrenergic receptors of asthmatic patients. *Chest* 69:479–83
42. Holgate, S. T., Tattersfield, A. E. 1976. Resistance to beta adrenergic agonists. *Thorax* 31:488–89
43. Simonsson, B., Svedmyr, N., Skoogh, B-E., Andersson, R., Bergh, N. P. 1972. *In vivo* and *in vitro* studies on alpha receptors in human airways. Potentiation with bacterial endotoxin. *Scand. J. Respir. Dis.* 53:227–36
44. Patel, K. R., Kerr, J. W. 1975. Alpha receptor blocking drugs in bronchial asthma. *Lancet* 1:348–49
45. 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. *J. Allergy Clin. Immunol.* 57:285–92
46. Cebezas, G. A., Graf, P. D., Nadel, J. A. 1971. Sympathetic versus parasympathetic nervous regulation of airways in dogs. *J. Appl. Physiol.* 31:651–55
47. Severinghaus, J. W., Stupfel, M. 1955. Respiratory dead space increase following atropine in man, and atropine, vagal or ganglionic blockade and hypothermia in dogs. *J. Appl. Physiol.* 8:81–87
48. Simonsson, B. G., Jacobs, F. M., Nadel, J. 1967. Role of autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airway disease. *J. Clin. Invest.* 46:1812–18
49. Cropp, G. 1975. The role of the parasympathetic nervous system in the maintenance of chronic airway obstruction in asthmatic children. *Am. Rev. Respir. Dis.* 112:599–605
50. Baigelman, W., Chodosh, S. 1977. Bronchodilator action of the anticholinergic drug, ipratropium bromide (Sch 1000) as an aerosol in chronic bronchitis and asthma. *Chest* 71:324–28
51. Ruffin, R. E., Fitzgerald, J. D., Rebuck, A. S. 1977. A comparison of the bronchodilator activity of Sch 1000 and salbutamol. *J. Allergy Clin. Immunol.* 59:136–41
52. Chan-Young, M. 1977. The effect of Sch 1000 and disodium cromoglycate on exercise-induced asthma. *Chest* 71:320–23
53. Gross, N. R. 1975. Sch 1000: A new anticholinergic bronchodilator. *Am. Rev. Respir. Dis.* 112:823–28
54. Herrmann, G., Aynesworth, M. B. 1937. Successful treatment of persistent extreme dyspnea (status asthmaticus). Use of theophylline ethylenediamine (aminophylline U.S.P.) intravenously. *J. Lab. Clin. Med.* 23:135–48
55. Austen, K. F. 1974. Reaction mechanisms in the release of mediators of immediate hypersensitivity from human lung tissue. *Fed. Proc.* 33:2256–62
56. Jenne, J. W., Wyze, E., Rood, F. S., MacDonald, F. M. 1972. Pharmacokinetics of theophylline. *Clin. Pharmacol. Ther.* 13:349–60
57. Thompson, R. D., Nagasawa, H. T., Jenne, J. W. 1974. Determination of theophylline and its metabolites in urine and serum by high-pressure liquid chromotography. *J. Lab. Clin. Med.* 84:584–93
58. Mitenko, P., Ogilvie, R. I. 1972. Rapidly achieved plasma concentration plateaus with observations on theophylline kinetics. *Clin. Pharmacol. Ther.* 13: 329–35
59. Sitar, D. S., Piafsky, K. M., Rangno, R. E. 1974. Analysis of plasma theophylline concentrations by high pressure liquid chromotography. *Clin. Res.* 22: 726A
60. Levy, G., Ellis, E., Koysooko, R. 1974. Indirect plasma-theophylline concentration in saliva. *Pediatrics* 53:873–76
61. Piafsky, K. M., Ogilvie, R. I. 1975. Dosage of theophylline in bronchial asthma. *N. Engl. J. Med.* 292:1218–22
62. Mitenko, P. A., Ogilvie, R. I. 1973. Rational intravenous doses of theophylline. *N. Engl. J. Med.* 289:600–3
63. Maselli, R., Casal, G. L., Ellis, E. F. 1970. Pharmacologic effects of intravenously administered aminophylline in asthmatic children. *J. Pediatr.* 76: 777–82
64. Soifer, H. 1957. Aminophylline toxicity. *J. Pediatr.* 50:657–59
65. Cox, J. S. G. 1970. In *Disodium Cromoglycate in Allergic Airways Disea e,* ed. J. Pepys, A. W. Frankland, pp. 13–27. London: Butterworths. 208 pp.
66. Brogden, R. N., Speight, T. M., Avery, G. S. 1974. Sodium cromoglycate (cromolyn sodium): A review of its mode of action, pharmacology, therapeutic efficacy and use. *Drugs* 7:164–282

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

67. Bell, J. H., Hartley, P. S., Cox, J. S. G. 1971. Dry powder aerosols. I. a new powder inhalation device. *J. Pharm. Sci.* 60:1559–64
68. Lichtenstein, L. M. 1973. *Asthma: Physiology, Immunopharmacology and Treatment*, ed. K. F. Austen, L. M. Lichtenstein, pp. 91–111. New York: Academic. 324 pp.
69. Karlin, J. 1972. The use of antihistamines in asthma. *Ann. Allergy* 30: 342–47
70. Popa, V. 1977. Bronchodilating activity of an H1 blocker, chlorpheniramine. *J. Allergy Clin. Immunol.* 59:54–63
71. Nakazawa, T., Toyoda, T., Furukawa, M., Taya, T., Kobayashi, S. 1976. Inhibitory effects of various drugs in dual asthmatic responses in wheat flour-sensitive subjects. *J. Allergy Clin. Immunol.* 58:1–9
72. Sly, R. M., Matzen, K. 1974. Effect of diethylcarbamazine pamoate upon exercise-induced obstruction in asthmatic children. *Ann. Allergy* 33:138–44
73. Koivikko, A. 1973. Diethylcarbamazine in bronchial asthma. *Ann. Allergy* 31:45–46
74. Piper, P. J., Vane, J. R. 1969. Release of additional factors in anaphylaxis and its antagonism by anti-inflammatory drugs. *Nature* 223:29–35
75. Mathé, A. A., Levine, L. 1973. Release of prostaglandins and metabolites from guinea pig lung. Inhibition by catecholamines. *Prostaglandins* 4:887–90
76. Pasargiklian, M., Bianco, S., Allegra, L. 1976. See Ref. 3, pp. 461–75
77. Mathé, A. A., Hedqvist, P. 1975. Effect of prostaglandins F_{2a} and E_2 on airway conductance in healthy subjects and asthmatic patients. *Am. Rev. Respir. Dis.* 111:313–20
78. Smith, A. P., Cuthbert, M. F., Dunlop, L. S. 1975. Effects of inhaled prostaglandins E_1, E_2 and F_{2a} on airway resistance of healthy and asthmatic man. *Clin. Sci. Mol. Med.* 48:421–30
79. Shenfield, G. M., Clarke, M. E., Patterson, J. W. 1975. Interaction of corticosteroids and catecholamines in the treatment of asthma. *Thorax* 30:430–35
80. Ellul-Micallef, R., Fenech, F. F. 1975. Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. *Lancet* 2:1269–71
81. Ellul-Micallef, R., Borthwick, R. C., McHardy, G. J. R. 1974. The time course of response to prednisolone in chronic bronchial asthma. *Clin. Sci. Mol. Med.* 47:105–17
82. Wilson, A. F. 1977. Drug treatment of acute asthma. *J. Am. Med. Assoc.* 237:1141–43
83. Cope, C. 1972. *Adrenal Steroids and Disease*, pp. 488–91. Philadelphia: Lippincott. 833 pp. 2nd ed.
84. Syntex Research 1976. *Monograph for Clinical Investigation of Cloprednol*, p. 5
85. Kaufman, H., Bruderman, I., Gelbard, C., Schey, G. 1976. Evaluation of pituitary-adrenal function in patients with chronic bronchial asthma following substitution of steroid treatment with disodium cromoglycate (lomudal). *J. Allergy Clin. Immunol.* 57:267–77
86. Brooks, S. M., Werk, E. E., Ackerman, S. J., Sullivan, I., Thrasher, K. 1972. Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N. Engl. J. Med.* 286:1125–28
87. Dwyer, J., Lazarus, L., Hickie, J. B. 1967. A study of cortisol metabolism in patients with chronic asthma. *Australas. Ann. Med.* 16:297–304
88. Br. Thorac. Tuberc. Assoc. 1976. A controlled trial of inhaled corticosteroids in patients receiving prednisone tablets for asthma. *Br. J. Dis. Chest* 70:95–103
89. Brogden, R. N., Pinder, R. M., Sawyer, R., Speight, T. M., Avery, G. S. 1975. Beclomethasone diproprionate inhaler: A review of its pharmacology, therapeutic value and adverse effects. I. Asthma. *Drugs* 10:166–210
90. Girard, J. P., Vonlanthen, M. C., Heimlich, E. M. 1975. Therapeutic index of steroid aerosols in asthma. *Acta Allergol.* 30:363–74
91. Stewart, B. N., Block, A. J. 1976. A trial of aerosolized theophylline in relieving bronchospasm. *Chest* 69:718–21
92. Choo-Kang, Y. F. J., Grant, I. W. B. 1975. Comparison of two methods of administering bronchodilator aerosol to asthmatic patients. *Br. Med. J.* 2: 119–20
93. Morrow, P. E. 1974. Aerosol characterization and deposition. *Am. Rev. Respir. Dis.* 110:88–99
94. Riley, D. J., Weitz, B. W., Edelman, N. H. 1976. The responses of asthmatic subjects to isoproterenol inhaled at differing lung volumes. *Am. Rev. Respir. Dis.* 114:509–15
95. Dashe, C. K., Ponte, R. A., Ganapes, C. M., Drage, C. W., Kronenberg, R. S. 1974. The distribution of nebulized isoproterenol and its effect on regional ven-

tilation and perfusion. *Am. Rev. Respir. Dis.* 110:293–300
96. Chang, N., Levison, H. 1972. The effect of a nebulized bronchodilator administered with or without intermittent positive pressure breathing on ventilatory function in children with cystic fibrosis and asthma. *Am. Rev. Respir. Dis.* 106:867–72
97. McFadden, E. R. Jr., Lyons, H. A. 1968. Arterial blood gas tension in asthma. *N. Engl. J. Med.* 278:1027–32
98. Knudson, R. J., Constantine, H. P. 1967. An effect of isoproterenol on ventilation perfusion in asthmatic versus normal subjects. *J. Appl. Physiol.* 22:402–6
99. Palmer, K. N. V., Legge, J. S., Hamilton, W. F. D., Diament, M. L. 1969. Effect of a selective beta adrenergic blocker in preventing falls in arterial oxygen tension following isoprenaline in asthmatic subjects. *Lancet* 2:1092–94
100. Palmer, K. N. V., Legge, J. S., Hamilton, W. F. D., Diament, M. L. 1970. Comparison of effect of salbutamol and isoprenaline on spirometry and blood gas tensions in bronchial asthma. *Br. Med. J.* 2:23–24
101. Legge, J. S., Gaddie, J., Palmer, K. N. V. 1971. Comparison of two oral selective beta$_2$ adrenergic stimulant drugs in bronchial asthma. *Br. Med. J.* 1:637–39
102. Fitchett, D. H., McNichol, M. W., Riordan, J. F. 1975. Intravenous salbutamol in management of status asthmaticus. *Br. Med. J.* 1:53–55
103. Harris, L. 1973. Comparison of cardiorespiratory effects of terbutaline and salbutamol aerosols in patients with reversible airways obstruction. *Thorax* 28:592–95
104. DaCosta, J., Hedstrand, Y. 1970. The effect of a new sympathomimetic beta receptor stimulating drug (terbutaline) on arterial blood gases in asthma. *Scand. J. Respir. Dis.* 51:212–15
105. Harris, L. 1974. Comparison of cardiorespiratory effects of rimeterol and terbutaline aerosols. *Bull. Physiol. Pathol. Respir.* 10:801–10
106. Rees, H. A., Millar, J. S., Donald, K. W. 1967. Adrenaline in bronchial asthma. *Lancet* 2:1164–67
107. Rees, H. A., Borthwick, R. C., Millar, J. S., Donald, K. W. 1967. Aminophylline in bronchial asthma. *Lancet* 2:1167–69
108. Chick, T. W., Nicholson, D. P., Johnson, R. L. 1973. Effects of isoproterenol on distribution of ventilation and perfusion in asthma. *Am. Rev. Respir. Dis.* 107:869–73
109. Hales, C. A., Kazemi, H. 1974. Hypoxic vascular responses of the lung: Effect of aminophylline and epinephrine. *Am. Rev. Respir. Dis.* 110:126–32
110. Godfrey, S., König, P. 1976. Inhibition of exercise-induced asthma by different pharmacological pathways. *Thorax* 31:137–43
111. König, P., Jaffe, P., Godfrey, S. 1974. The effect of corticosteroids on exercise-induced asthma. *J. Allergy Clin. Immunol.* 54:14–19

Annu. Rev. Pharmacol. Toxicol. 1978.18:541-561. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.