LITERATURE REVIEW

Recent Advances in Childhood Asthma

by

SUDIGDO SASTROASMORO

(Department of Child Health, Medical School, University of Indonesia, Jakarta)

Abstract

Research in bronchial asthma shows striking advances in the last fifteen years.

In recent years, advances in immunology and the introduction of beta adrenergic theory (neuro-humoral theory) lead to a new and comprehensive understanding on the pathogenesis and pathophysiology of asthma.

Physiological changes in asthma are particularly concerning the affection of smaller air ways, the goal of the newer methods is to find the most sensitive and reliable method to detect small airway alteration.

The current advances in the treatment of asthma are the sympathomimetic amines and the related compounds. The use of steroid, sodium cromoglycate and immunotherapy will be reviewed in this paper.

Received 14th. January 1980.

Introduction

Research in bronchial asthma shows striking advances in the last fifteen years. Advances in immunology and the introduction of beta adrenergic theory of bronchial asthma (Szentivany, 1968) lead to a new and comprehensive understanding on the pathogenesis and pathophysiology of asthma. In the field of management, many new drugs have been introduced, notably newer sympathomimetic amines, cromolyn sodium and inhaled steroids. Yet there still many questions should be answered and continous improvement in the management should be explored to overcome this important disease suffered by millions of children all over the world.

Terminology and Classification

Based on data available at present, asthma can not be defined precisely. Many authors used their own definitions in accordance with the subject discussed and their main interests. Additional knowledge and valuable informations in many aspects of asthma 'have lengthened rather than shortened the definition' (Bergher and Kass, 1972). The earlier definition of the AMERICAN THORACIC SOCIETY (1962) is still considered to be valid by most authorities because of its flexibility. According to the society, asthma may be defined as 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.

For many years asthma is classified as extrinsic and intrinsic. In extrinsic asthma, the cause of bronchoconstriction can be detected, usually with positive skin test. If the cause can not be detected, and the skin test is negative, then it is classified as intrinsic or infectious asthma. Recently Tuft (1977) objected these terms because of reasons : (1) too much reliance is placed on skin test result as the sole arbiter of classifying the disease, and (2) once asthma is said to be intrinsic, little or nothing further is done to find other possible cause or causes. He recommended to use term 'allergic asthma' if allergy is proved to be a factor. If the patient has all clinical features of asthma, and no specific factor can be elicited despite complete study, then it should be called 'bronchial asthma, cause undetermined' or chial asthma, cause undetermined' or group, the vast majority of asthmatic patients (95%) are of extrinsic type (Dickson, 1973).

Godfrey (1977) has proposed a clinical classification of childhood asthma which has proven to be useful in clinical practice (Table 1).

TABLE 1 : *Classification of childhood asthma*

Group	Clinical Course	Regular Treatment	% In Hospital Clinic
A	mild intermittent	intermittent broncho-dilators	31
B	severe intermittent	intermittent 'crash' oral steroids	7
C	moderate perennial	cromolyn sodium or equivalent	34
D	severe perennial	aerosol steroids	25
E	very severe	oral steroids	3

From Clark, T.J.H. and Godfrey, S. : Asthma. (Chapman and Hall, London, 1977).

Pathogenesis and Pathophysiology of Asthma : Current Concepts

It is clear in recent years that asthma can not be exclusively considered as immunologic disease. Other factors than allergen can induce bronchospasm in susceptible individuals, including chemical, infectious, emotional and physical factors. This lead to consider asthma in a broader concept.

Immunologic Considerations

The immunologic basis of atopic asthma is type I (IgE mediated) hypersensitivity reaction. This involves the sensitization of mast cells located beneath the respiratory mucosa, basophils and possibly eosinophils containing IgE in its membrane by the allergen. This interaction will result in degranulation of such cells and release agents so-called mediators of anaphylaxis i.e. histamine, serotonin, slow reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), various kinins and prostaglandins (Levison et al., 1974; Rebuck 1975). These agents stimulate vagal afferents resulting in reflex bronchoconstriction, directly contact bronchial smooth muscles, increase capillary permeability and draw eosinophils to the site of injured tissue (Levison et al., 1974).

Eosinophil, which is drawn to the site of allergic injury by ECF-A, previously thought to have phagocytic role, and has recently known to elaborate 2 specific enzymes to neutralize certain mast

cell products. First histaminase is specific for histamine and the second enzyme, arylsulfatase is specific for SRS-A (reviewed by Warren, 1976; Tjokronegoro, 1977).

The IgE (reaginic antibody) is present in the sera of both allergic and nonallergic individuals (Ishizaka and Ishizaka, 1970), but in allergic asthma IgE concentration is almost consistently higher than normal population. Grove and associates (1975) demonstrated that the mean serum IgE level in patients with asthma was 225 units/ml in contrast to 98 units/ml in normal control. Similar result was also reported by Lin et al., (1977) who obtained that 23 out of 35 (65%) patients with asthma showed increased serum IgE concentration. Turner, Sumarmo and Matondang Siahaan (1978) confirmed this finding in Indonesian asthmatic children. Serum IgE level in the newborn correlates well with the development of atopic disorder later in life (Kjellman and Johanson, 1976), however, extrinsic and intrinsic asthma can not be differentiated solely by IgE measurement (Grove et al., 1975).

Elevated serum IgE is not only found in atopic disorders; many other diseases show total IgE elevation as seen in Table 2 (reviewed by Yunginger and Gleich, 1975).

TABLE 2 : *Diseases reported to be associated with elevated total serum IgE values*

Diagnosis	Relative Degree of IgE Elevation
Seasonal allergic rhinitis	+ to ++
Extrinsic bronchial asthma	++
Atopic dermatitis	++++
Bronchopulmonary aspergillosis	++++
Chronic acral dermatitis	++++
Bullous pemphigoid	++
Thymic alymphoplasia	++
Wislott — Aldrichy Syndrome	
Parasitic infections	
Ascariasis	+++
Visceral larva migrans	+++
Capillariasis	+++
Paragonimiasis	+++
Fasciolasis	+++
Schistosomiasis	++
Hookworm	++
Trichinosis	++

After Yunginger, J.W. and Gleich, G.J.. : The impact of the discovery of IgE on the practice of allergy. Pediat. Clin. N. Amer. 22 : 3 (1975).

There are other observations in immunologic aspects of asthma. In asthmatic patients, particularly if correlated with respiratory tract infection, serum IgA is low (Geller Berntein et al., 1976; Baker et al., 1976; Grove et al., 1975). Grove et al., also found an increased IgG, while Lin et al., (1977) reported increased IgM concentration in their series. Neuman and Creter (1977) found that inherited defect of complement system may cause intrinsic asthma via the kinin system. In children with asthma the alpha-1-antitrypsin serum levels are higher in non steroid dependent asthma whereas in steroid dependent asthma the level of this antiinflammatory protein of the respiratory tract are normal (Schwartz et al., 1977).

Although some authorities (Ghazanshahi et al., 1976) believe that T-lymphocytes in asthmatic children are depressed, Brasher et al., (1977) did not confirm this; they found T-lymphocytes in 76 children with asthma and allergic rhinitis were not significantly different when compared with non atopic children.

Type I allergic reaction is not a sole immunologic pathogenesis in asthma, Pepys (1973) reviewed that type III allergic reaction (immune complex) may play a role in the pathogenesis of some asthmatic subjects. Type III reaction, also known as Arthus phenomenon, involves the interaction between antigen and circulating precipitin (IgM, IgG), complements (especially C_3a and C_5a) and polymorphonuclear leukocytes, resulting the release of liberated lysosomes. This process may explain the delayed reaction (6 to 8 hours after challenge) following period of recovery after the immediate bronchoconstriction in some subjects.

The degranulation of mast cells and basophils may also occur independently of IgE-antigen reaction, but via the direct activity of HRF (histamine releasing factor), which is identical to the split complement fragment C_5a. This finding may explain some clinical observations of asthma for which a sensitivity basis has been suspected but never proved (Warner, 1977; Tjokronegoro, 1977).

Although it is obvious that types I and III allergic reactions play an important role in the pathogenesis of allergic asthma, there is still another question i. e. why in a patient with clear cut allergic cause, attacks may be precipitated by non allergic stimuli such as exercise, emotional and physical stimuli. Vane (cited by Dickson, 1973) has demonstrated that non allergic stimuli such as gentle massage of the lung surface releases the mediators of anaphylaxis. Junod (1975) stated that hypoxia can also result in the release of mediators.

So far, intrinsic asthma has not been proved to have any correlation with immune or allergic aspects. The beta adrenergic theory of bronchial asthma may explain the pathogenesis of intrinsic as well as extrinsic asthma.

Beta adrenergic theory of bronchial asthma

This theory was introduced by Szentivanyi in early 1960's and on subsequent occasions, and has been comprehensively summarized on his monumental article : 'The beta adrenergic theory of the atopic abnormality in bronchiall asthma' (Szentivanyi, 1968).

Adrenergic receptors comprise two receptors, alpha and beta-receptors. Stimulation of the receptors by catecholamine, which is released under the influence of sympathetic nervous system, results in bronchoconstriction (alpha-receptors) and bronchodilation (beta-receptors). The beta adrenergic theory proposes that the responsiveness of beta-adrenergic receptors of the tracheobronchial tree, including those of smooth muscles, is diminished; it can not exert a homeostatic bronchodilating effect against bronchoconstriction as normally should be (Nelson, 1975). Szentivanyi asserts that adenylcyclase, the enzyme presents in all animal cells except mature erythrocyte, is the beta adrenergic receptor. The function of adenylcyclase is, in the presence of magnesium ions, catalyzing the formation of cyclic adenosine 3′5′-monophosphate (cAMP) from adenosine triphosphate (ATP). Cyclic AMP then mediates the mechanical activities of the muscle cells; in the case of bronchus, the result is bronchodilation. Cyclic AMP is broken down to 5′ AMP under the influence of enzyme phospodiesterase.

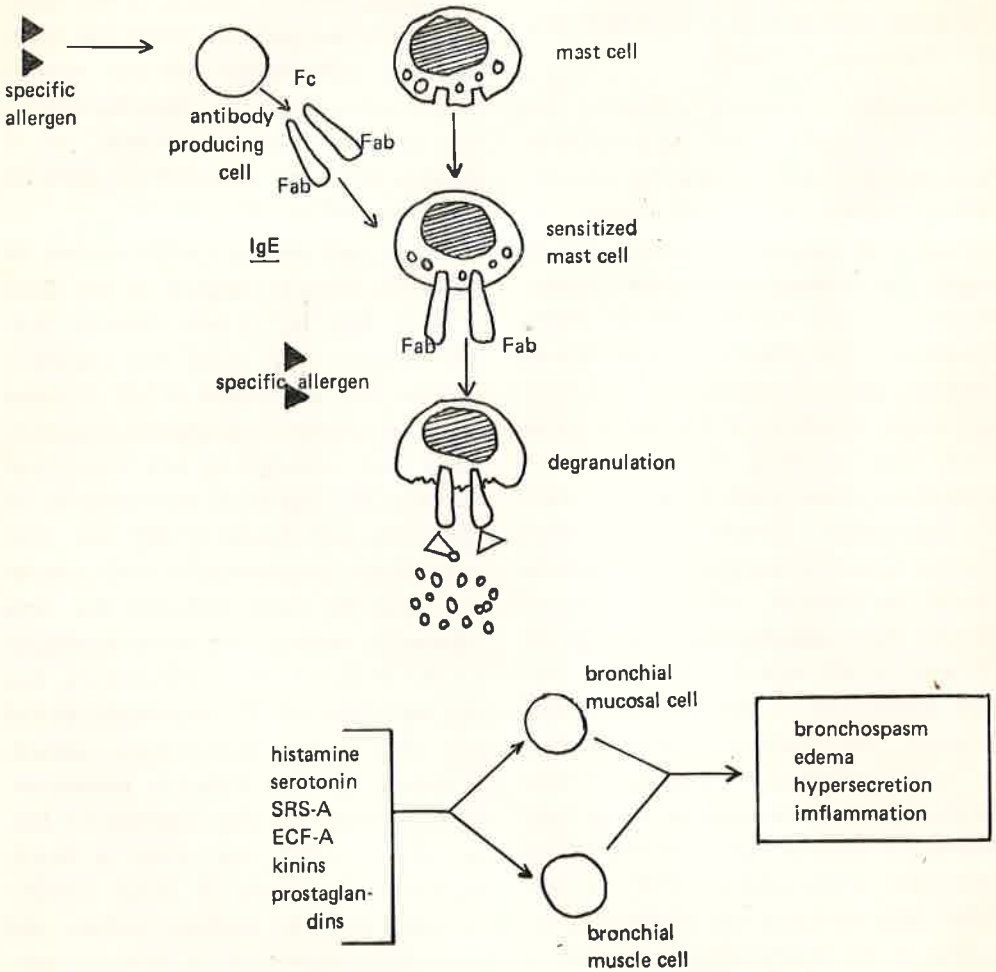
The fundamental abnormality in asthma is the inherited or acquired deficiency of adenylcyclase or blockade of its function; so the equilibrium between alpha and beta-receptors, which is normally in the favor of beta-receptor, is impaired. This leads to an imbalance of autonomic nervous control of the bronchi which are partially under the influence of sympathetic nervous system, resulting in excessive bronchoconstriction to a wide variety of stimuli, one of these is abnormal immunologic stimulus (Dickson, 1973).

Apold and Aksnes (1977) studied 24 asthmatic patients ranging in age from 6 to 14 years and 16 non asthmatic control subjects. They noted that asthmatic children had diminished cAMP response after subcutaneous epinephrine injection. They also observed a well correlation between the degree of the reactivity to histamine and plasma cAMP rise after epinephrine administration, and concluded that the more defective the beta adrenergic activity, the more hyperactive the bronchi. This phenomenon was not only observed in symptomatic period but also during asymptomatic period. It means that the defect is permanent. Similar result was also reported by Jenne et al., (1977) who found a highly significant reduction of urine cAMP/creatinin ratio in extrinsic asthma and moderately significant in intrinsic asthma, indicating beta impairment in this disease. They postulated what other investigators had thought of, that in extrinsic asthma there is an impairment

of cellular beta response, particularly those involving generation of cAMP aside of altered respiratory immunity affecting IgE responses to various stimuli.

In short, the beta adrenergic theory (neuro-humoral theory) of bronchial asthma may be summarized as follows:

FIG. 1 : *Schematic representation of the pathogenesis of asthma.*



(1) The basic abnormality of bronchial asthma is bronchial hyperreactivity to various stimuli including immunologic, psychic, chemical, infectious and physical stimuli.

(2) This hyperreactivity results from either deficiency or blockade of adenylcyclase, the beta receptor activity.

Pulmonary Pathophysiology in Asthma

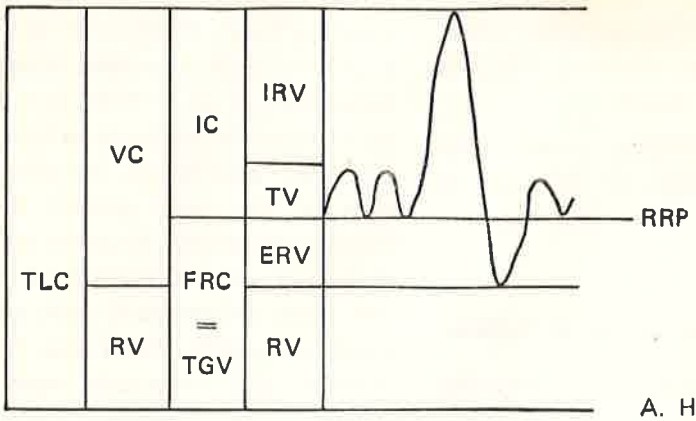
The conventional triad of airway changes in asthma are bronchospasm, mucosal edema and bronchial hypersecretion. But actually the alteration is not so simple as such. Thickening of basement membrane, glandular hyperplasia, intraluminal obstruction by cellular debris and inflammatory exudate and airway collapse are almost invariably present in asthma. In recent years, the pathologic physiology of asthma has been more concerned with lesions in peripheral airways (less than 2 mm in diameter) rather than in larger airways. Indeed this is an important point of consideration, because many patients died of asthma had mucus plugging in small airways as the most striking finding (Dunhill, 1960 as cited by Rebuck, 1975). This statement was confirmed by Wood and Lecks (1976) who reviewed the cause of death in 7 children with asthma, and found that mucus plugging in the smaller airways was found in all cases. The plugging was so extensive that they were not surprised that the patient had died, but that 'they had survived so long'. Postmortem findings in 8 children died of asthma reviewed by Buranakul et al., (1974) also showed thick mucus in tracheobronchial tree in all cases. Microscopic examination in most of the cases showed bronchial muscle hypertrophy, basement membrane thickening and infiltration of bronchi with acute inflammatory cells, predominantly eosinophils. Focal area of hyperinflation and atelectasis were found elsewhere.

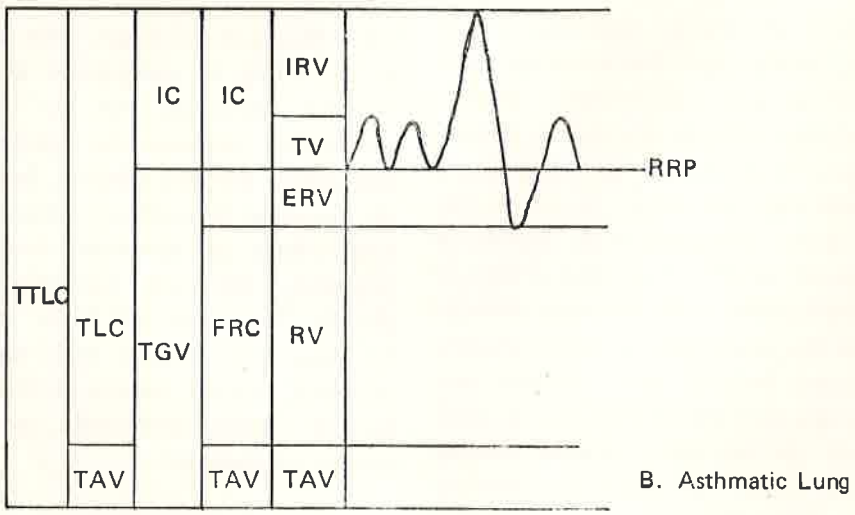
In initial attacks, expiratory obstruction leads to hyperinflation (airtrapping) which is usually bilateral and symmetrical (Richard and Siegel, 1969; Levison et al., 1974) to compensate decreased alveolar ventilation. As the bronchoconstriction increases, the compensatory mechanism will not effective, leading to the increase of residual volume, total lung volume and functional dead space, producing decreased pulmonary compliance. The additional force obtained by accessory muscles will result in increased thoracic tension to cause closure of smaller bronchioles, producing further obstruction.

Pulmonary Function Testing in Asthma

The decrease in the elastic recoil (pulmonary compliance) as described above makes the change of the respiratory volume as seen in Fig. 2.

FIG. 2: *Changes of respiratory volume in asthma.*





Abbreviations : TLC = Total Lung Capacity; VC = Vital Capacity; RV = Recidual Volume; IC = Inspiratory Capacity; IRV = Inspiratory Reserve Volume; TV = Tidal Volume; ERV = Expiratory Reserve Volume; RRP = Resting Respiratory Positon; TTLC = True Total Lung Capacity; TGC = Thoracic Gas Volume; FRC = Functional Recidual Capacity.

Detection of airway obstruction

Many sophisticated methods of pulmonary function testing have been introduced in recent years, both to evaluate physiological changes and to assess therapeutic effect of bronchodilators. Since physiological changes in asthma are particularly concerning the affection of smaller airways, the goal of the newer methods is to find the most sensitive and reliable way to detect small airway alterations, but it seems that there are still some controversies on this particular problem, The clinician will find only little, if any, difficulty to diagnose asthma. But if this will be confirmed by spirometric measurements by the help of the physiologist, the latter not infrequently fails to give such support (Sobol and Emirgil, 1976). If the physiologist could establish evidence of bronchoconstriction and that the bronchoconstriction is reversible, then the clinician could take the benefit. But if such evidence is not confirmed, the diagnosis of asthma can not be ruled out.

Payne and others (1967) believed that the most precise method in evaluating airway responsiveness is a body plethysmograph. Other authors pointed out that several values derived from spirometry such as FEV (forced expiratory volume), FEV_1 (forced expiratory volume in 1 second), PEFR (peak expiratory flow rate), MMEFR (maximal mid-expiratotory flow rate), Gaw (airway conductance) and Raw (airway resistance) have valuable meaning in assessing airway obstruction as well as its responsiveness to bronchodilator therapy. But such statement is not without conflict.

TABLE 3 : *Some spirometric measurements to assess airway obstruction.*

Measurement	Location of obstruction
FVC	large and small airways
FEV_1	large and small airways
FEV_1/FVC	large and small airways
SGaw	large airways
Raw	large airways
PEFR	large airways
MMEFR	small airways
Cdyn	small airways
TAV	small airways

Abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second (timed vital capacity); S Graw = specific airway conductance; Raw = air way resistance; PEFR = peak expiratory flow rate; MMEFR = maximal midexpiratory flow rate; Cdyn = dynamic compliance; TAV = trapped air volume.

Adapted and simplified from Souhrada, J.F. and Bucklev, J.M. : Pulmonary function testing in asthmatic children. Pediatr. Clin. N. Amer. 23 : 249 (1976).

Tinkelman, Avner and Cooper (1977) stated that although FEV_1 and MMEFR have a good correlation with clinical improvement as asthmatic subjects receiving bronchodilator, their value is more indicate how the pulmonary function reaches predicted normal value rather than how it changes to baseline levels. Study of Light, Conrad and George (1977), however, proved that FEV_1 is the one best test in evaluating bronchodilator effectiveness. Furthermore, Leifer and Wittig (1977) found that MMEFR can not be used as a sole index of bronchodilator response.

It must be emphasized that, due to technical reasons, i.e. cooperation of patient in performing repeated spirometric procedures, pulmonary function is particularly difficult to perform in small children. Most studies were conducted in older children and adult subjects. Some popular spirometric measurements to asses bronchial obstruction are listed in Table 3.

Etiologic Factors in Childhood Asthma

Asthma is quite a complex disease. It is influenced by many factors; some of them are still obscure, other factors have been proved by means of statistical survey but no explanation have been done satisfactorily. The following paragraphs will describe some recent observations on this particular matter, most of them have been suggested by previous authors many years before.

The majority of asthmatic children are of extrinsic type, where positive skin test can usually be demonstrated. It is reasonable, therefore, to assume that external allergens play an important role in childhood asthma. The most important allergen commonly found elsewere is the house dust.

This material contains a mixture of substance from breakdown products of furniture, carpets, the house-dust mite, molds and animal as well as human dander. Of these, house-dust mite is considered to be the most allergenic in most part of the world (Morita et al., 1975).

Two species of house- dust mite Dermatophagoides have been extensively studied. D. pteronyssinus and D. farinae (Collin-Williams, Hung and Bremner, 1976). These mites particularly like beds because of the large source of human dander (Flod, Franz and Galant 1976). Recent study of Turner, Sumarmo and Matondang-Siahaan (1978) indicated that D. pteronyssinus plays an important role in asthma and allergic rhinitis in Indonesian children. This finding supports the previous data (Matondang-Siahaan, 1977).

Other important external allergens are pollens and animal feathers. This should be carefully considered when we are facing asthmatic children, since the most important procedure in every stage of asthma is avoidance to the offending allergens whenever possible.

Food is often underestimated as the possible factor in asthma. Two studies have shown that food is the major etiologic factor in asthmatic children under

2 years of age. Brasher (1976) analyzed 83 infants with asthma found that more than 50% of them had relieved from their symptoms during the trial of hypoallergic diet. It was also noted that the younger the infant, the more prominent the role of food in precipitating asthma. The increase of allergen-specific antibody against house dust animal dander and pollens indicated that such inhalants which are considered as the major factor in childhood asthma, have a limited role in infantile asthma. More impressive figure has been reported recently by Ogle and Bullock (1977). In their series consisting of 188 asthmatic patients under 1 year of age, they found almost complete improvement and significant improvement in 62% and 28%, respectively (overall good result 90%) after hypoallergic diet. However, 70% of them, later developed significant inhalant allergy to house dust, molds and pollens. Again, this study showed that food (milk, chocolate, egg, corn, citrus etc) is quite frequent causing asthmatic symptoms in infantile asthma while inhalants are particularly important in older children.

The introduction of cow's milk, especially in the first week of life will result in the increase development of atopic disorders later in the life (Hill, 1976; Blair, 1977). Wittig et al., (1978) found that breast fed infants had a significantly later onset of allergic disease than bottle fed patients (average 7.1 vs. 4.5 years, $p<0.0001$). This should lead further support to the value of breast feeding in infancy.

Respiratory tract infection is other important factor in childhood asthma. Brasher (1976) found that 25 out of 83 asthmatic infants had roentgenographycally documented episodes of pulmonary infiltrate, compared with 9 out of 71 control infants. The association of viral infection and wheezing is well documented, albeit poorly explained. Mitchell, Inglis and Simpson (1976) have isolated virus in 14.2% of their series. The most frequent was rhinovirus, followed by respiratory syncitial virus and adenovirus. They also noted that wheezing attacks were more severe when associated with viral infection. The association between bronchiolitis,, which is chiefly caused by respiratory syncitial virus with the development of asthma is well documented; a considerable percentage of infants who had bronchiolitis would develop asthma in their childhood.

The role of anesthesia and surgery as the predisposing factors in childhood allergic disease is still controversial. A report of group from Rochester (Johnstone, Roghman and Pless, 1975) implicated pyloric stenosis surgery and herniorraphy during infancy as significant predisposing factors in the development of asthma and hay fever in childhood. Although their methods are open for criticism because they used telephone and questionnaire to parents, the result was quite impressive. The prevalence of asthma in their series with pyloric stenosis was 18%, that of hay fever was 23% and that of asthma, hay fever or both was 35%, in contrast to a

random sample of the same country which showed 3.4% with asthma, 8.5% with hay fever and 10.6% with either. Higher figures were found in post herniorraphy patients. On the other hand Brasher (1976) only found 9 out of 83 patients who had undergone surgery, and 7 of these nine were having episode of wheezing before they had undergone general anesthesia.

There are many other factors that could be considered as predisposing or precipitating factors in asthma, including physical exercise, climate, many drugs and chemicals. The role of phychological factor should not be overlooked (Mattson, 1975). Study of Maijer (1976) emphasized the role of social status in asthma. He reported that the mother's low level of education had a role in the development of asthmatic symptoms, while the father's education had not. Socioeconomic level was said not to have a role in this disease, but it should be interpreted in the context Maijer used. In addition, he noted that infantile eczema persisting beyond the age of 2 is closely associated with childhood asthma.

More studies are needed to establish other etiologic factors (some authors prefer to use term risk factor) in asthma, and each of it would need proper explanation. However, the risk of controversial observation seems well exist. For example a transient deficiency of IgA during early infancy was said to be an important factor in the development of atopic disease (Taylor et al., 1973), but other authors failed to confirm this statement (Brasher and Bourland, 1975).

Exercice-Induced Asthma (EIA)

Physical exertion might induce bronchoconstriction in both normal and asthmatic subjects. Early during exercise both subjects show evidence of bronchodilation, possibly due to sympathetic activity. After several minutes later, evidence of bronchoconstriction can be detected by means of subjective symptoms, physical signs and objective pulmonary function testing.

By definition, EIA is an acute, reversible, usually self limiting airway obstruction which develops after strenuous exercise in patients with asthma or hay fever. EIA is present in both extrinsic and intrinsic asthma, although in extrinsic asthma the bronchospasm is more severe and more prolonged than in intrinsic asthma. Eggleston (1975) studied 16 extrinsic and 6 intrinsic asthmatic children ranging in age from 7 to 18 years. After 5 minutes of jogging at 2.4 to 5.0 mph on a 10% to 15% grade, he found a 27% fall in FEV_1 in extrinsic asthmatic, while in intrinsic asthmatics the fall of FEV_1 was only 12% at 5 minutes. Significant difference in MMEFR was also noted. The severity of bronchoconstriction has seasonal variation; in extrinsic asthma the bronchoconstriction was more severe during pollen season.

Bierman, Kawabori and Pierson (1975) had shown non asthmatic subjects but with other atopic disorders had also sig-

nificant decrease in airway function after being challenged with exercise. As seen in Table 4 the incidence of EIA in asthmatic subjects was as high as 63%, while in atopic non asthmatic and control subjects were 41% and 7%, respectively.

Godfrey (1975) extensively reviewed the clinical and physiological implications of EIA. Amongst the important conclusions are :

(1) Type of exercise is important in inducing bronchoconstriction. Running is the most asthmogenic, followed by cycling, swimming and walking, even with the same metabolic stress.

(2) Duration of exercise also has an influence in EIA; the maximum effect being 6 to 8 minutes of running enough to raise the heart rate to 180 beat per minute in children or 140 per minute in adults.

TABLE 4 : *Incidence of EIA in asthmatic, atopic non asthmatic and control subjects*

	No. of subjects	Age	% of EIA
Asthmatic	134	5 — 18 years	63
Non Asthmatic, Atopic	102	5 — 18 years	41
Control	56	5 — 18 years	7

After Bierman, C.W., Kawabori, I. and Pierson, W.E.: Incidence of exercise induced asthma in children. Pediatrics 56 (Suppl) : 847 (1975).

The pathogenesis of EIA is remain in speculations. Evidence that EIA can be prevented by cromolyn sodium when given before the challenge (Silverman and Andrea, 1972; Godfrey, Silverman and Anderson, 1973; Chan-Yeung, 1977) suggest that EIA is produced by release of mediators of anaphylaxis during exercise. The role of parasympathetic nervous system in the pathogenesis of EIA has also been considered, since atropin, a parasympathomimetic agent, can prevent EIA (Jones et al., 1963; Tashkin et al., 1977).

While Godfrey did not believe that metabolic and blood gas factors play a role in the pathogenesis of EIA, Cropp (1975) has proposed the complicated hypothetical scheme involving sympathetic-parasympathetic nervous system, metabolic acidosis and acid-base alterations.

EIA can be prevented by various drugs such as theophylline, atropin, sympathomimetic amines, cromolyn sodium as well as indoramin, an alpha-adrenoceptor blocking agent as described by Bianco et al., (1974). It must be emphasized that the drugs should be given before the challenge. These phenomena and other aspects of EIA place EIA in a unique position; it might be used to study physiological and pharmacological mechanisms of asthma (Godfrey, 1975).

Aspirin Sensitive Asthma and Drug-Induced Bronchospasm

Aspirin (Acetylsalicylic acid, ASA), has been known can induce asthmatic attack more than 50 years ago. Samter and Beers (1968) reported that there was an almost consistent syndrome in non atopic asthmatic patients who had ASA intolerance and nasal polyps. This constellation of intrinsic asthma, ASA intolerance and nasal polyps has called 'ASA triad' (Snyder and Siegal, 1967).

Since aspirin is one of the most frequent drugs used freely without any physician's recommendation, this phenomenon has called attention of many authorities. One may ask whether the use of aspirin in asthmatic children should be avoided or not. This question is not easy to answer. There are reports that the prevalence of aspirin intolerance varied widely according to several authors, being as low as 0.4% to as high as 28%. Rachelefsky and others (1975) reported the incidence of ASA intolerance was 28% of 50 patients with intractable extrinsic asthmatics, and characterized by (1) a greater number of female, (2) an earlier onset of wheezing, and (3) more sinusitis than aspirin tolerance group. This finding adds previous reports that ASA intolerance was usually found in intrinsic asthma.

On the other hand Falliers (1974) studied 1,298 patients with asthma only found 6 cases who had family history of aspirin intolerance. Furthermore he concluded that atopic disease and ASA triad can affect the same individual without being necessarily related etiologically.

The exact mechanism of aspirin sensitive asthma is not fully known. Because the ingestion of aspirin may cause sudden occurrence of wheezing,urticaria and angioedema, one suggested that the underlying cause is type I allergic reaction. But subsequent studies had failed to confirm hypothesis. In recent years it is thought that the pathophysiology of ASA intolerance is through the influence of aspirin to prostaglandins. Two prostaglandins have been regularly found in the human lung, prostaglandin F2-alpha (PGF2-alpha) and prostaglandin E2 (PGE2). PGF2-alpha acts to induce bronchospasm on human tracheobronchial tree, while PGE2 is a bronchodilator (Abrishami and Thomas, 1977). Aspirin may influence prostaglandin synthesis and release. It is speculated that aspirin intolerance results when the equilibrium between PGE2 and PGF2-alpha is altered to the favor of PGF2-alpha. It has been found that asthmatic patients are abnormally sensitive to PGF2-alpha, but more variable response to PGE2. But another group (Orehek et al., 1977) reported that although PGF2-alpha may induce bronchospasm, aspirin sensitive asthmatic did not differ from patient with regular asthma in terms of their response to PGF2-alpha. This controversisal matter obviously needs further clarification.

Prince (1977) has called attention to tartrazine, one of the most widely artifi-

cial dyes used for medical preparations (pills, capsules, liquids) as well as foods and drinks. It was Lockey (1959, as cited by Prince) who first analyzed the molecular structure of tartrazine, which was similar to that of aspirin and might cause cross sensitivity in patients allergic to aspirin. This 'hidden allergen' should always borne in mind when we are facing a child with ASA intolerance.

Many other drugs have been known to cause bronchospasm. Kounis (1976) has tried to classify the probable pathogenesis of drug-induced bronchospasm as allergic reaction, idiosyncracy, pharmacologic action and local irritation. There is evidence that drugs in the treatment of asthma (sympathomimetics, corticosteroids, etc) may occasionally cause bronchoconstriction, either as the result of allergic reaction or of idiosyncracy. Due to its wide variety of drugs that may induce bronchospasm both in normal and asthmatic individuals, it is often difficult to ascertain what particular drug that cause the problem, especially if they are used in combinations.

Diagnostic Aids in Childhood Asthma

The diagnosis of asthma is established by case history and clinical findings. Certain tests however, may valuable in supporting the clinical diagnosis, and may be important to determine whether the disease should be classified as allergic or non allergic asthma.

Routine laboratory examinations

Eosinophilia is the only obvious changes that can be expected in routine laboratory work up in asthmatic children. Church and Richards (1978) found that 62.0% of their series showed eosinophilia, which was defined as absolute eosinophil count of more than 300 per cu mm. Nasal eosinophils were elevated in 47 out of 100 patients examined. Demonstration of Charcot-Leyden crystals and Curshman spirals are difficult to obtain in children with asthma.

Skin Tests

This is the most popular test used by both pediatricians and allergists to rule out the allergic basis of asthma. The test may be performed in 3 ways : (1) scratch test, which is the least sensitive and is employed to the severely sensitive patients; (2) prick test, which is approximately 5 to 10 times more sensitive than the scratch test, and (3) intradermal test which is 10 to 1000 times more sensitive than the prick test and is particularly valuable for low strength allergens (Aas, 1975).

Skin test is of limited value in infants and children under 3 years of age because the skin sensitivity to histamine is low in such subjects, as is in very old patients.

The antigen is introduced through the skin, and in the presence of IgE coating mast cells, the histamine is released leading to the typical wheal and flare response. The reaction is read at 20 minutes and size of reaction is assessed in relation to negative (saline) and positive (histamine) control. The result may be denoted as negative, + to + + + + positive.

The immediate reaction (type I Cell and Coomb's allergic reaction) will disappear gradually within 20 to 60 minutes. Late reaction that may appear after 1 - 4 hours and reacting its maximum at 6 to 24 hours may be observed, and this is believed to be diagnostic for type III allergic reactions due to interaction between antigen and precipitating antibodies.

Skin test is cheap, easy to do, rapid, convenient to the patient and in most instances it correlates well with challenge test (bronchial provocation test, nasal test) and in vitro testing (radioallergosorbent test, leukocyte histamine release). However, since skin test implies the sensitization of the skin, in the absence of clinical support, a positive skin test should never form the basis of any therapeutic decision (Czarny, 1976).

Challenge Tests

(a) Bronchial Provocation Test (BPT)

The principle of BPT is to challenge the patient with aerosolized allergen extracts or pharmacologically active fluids and control solution under observation and to registrate the effects on respiratory pattern and ventilatory capacity (Aas, 1975).

The test is initiated by the determination of basal FEV_1. The allergen extract or pharmacologically active fluid (e.g. histamine 0.1% solution) is then administered as an aerosol using a nebulizer at a flow rate approximately 10 L/minute for 1 minute, take approximately 15 deep breaths. A positive response is obtained when there is a fall in FEV_1 greater than 25% of basal reading (Dickson, 1973).

The immediate response that occurs within several minutes of the BPT is of short duration, resolving spontaneously and easily reversed by bronchodilators. However, many asthmatics, especially those of severe form, also have late airway obstruction beginning 4 to 6 hours after inhalation. This late reaction is usually more severe, more prolonged and is poorly responsive to bronchodilators. Warner (1977) found that nearly 75% of chronic asthmatic children who were allergic to the house-dust mite showed this late reaction, and there was a positive correlation between more severe clinical asthma and the occurrence of a late reaction on BPT.

BPT is not a routine procedure in the diagnosis of asthma. It is indicated when the accurate allergy diagnosis is a must, and is expected to have a consequence for the choice of therapy especially hyposensitization (Aas, 1975; Warren, 1976). In rare instances it may be used to confirm when the diagnosis of asthma in allergic child is in doubt despite complete study using other more convenient approaches.

(b) Nasal Test

This procedure is done by instillation the test substance in one nostril while the other is used as a control. The test is positive when after a few minutes the tested nostril becomes edematous, in-

creased watery secretion, itching and sneezing. The control side may remain normal for some time, but then slowly develops the same reaction. Positive nasal test is not diagnostic for allergic asthma unless the test is able to provoke bronchial obstruction (Aas, 1975).

(c) Exercise test

The purpose of this test is to demonstrate bronchial constriction after being challenged with strenuous physical exercise. The most simple test may be done in the office, by asking the child to run up and down stairs or around the office building for 6 to 8 minutes as fast as possible to raise the heart rate approximately 180 beats. Rough assessment can be made by repeated observation and chest auscultation over a half hour period. If spirometer is available, quantitative result may be obtained by comparing FEV_1 before and after the challenge. A 20 to 25 percent reduction in FEV measurement is reliable diagnostic for exercise - induced asthma (Dickson, 1973; Cropp, 1975).

In the laboratory detailed procedure may be undergone: Treadmill running for 6 to 8 minutes that increases heart rate to 180 per minute is the most useful, since it triggers bronchoconstriction easily. Pulmonary function testing should be performed repeatedly within the first 30 to 40 minutes after the challenge, and is usually expressed in per cent of pre exercise values. Drugs and other medications that may influence the test should be withheld in sufficient time before the test.

In Vitro Methods

Total serum IgE, as reviewed earlier, is non specific for allergic disorders. In recent years in vitro procedure which identify various IgE antibodies against specific allergens are much more important in the allergic diagnosis. Among the procedures, leukocyte histamine release (Hr) and radioallergosorbent test (RAST) are the most widely studied and used.

(a) Leukocyte Histamine Release (HR)

This procedure involves the addition of increasing quantities of allergen to a standard concentration of sensitized leukocyte at 37°C in Ca++ and Mg++ containing buffer, and the calculation of the percentage of cellular histamine released by the allergen. The amount of allergen required to cause the release of 50% of the total histamine is used as cellular sensitivity.

The method is specific, sensitive but expensive and time consuming, and requires fresh blood, hence it has limited application to clinical practice (Yunginger and Gleich, 1975).

(b) Radioallergosorbent Test (RAST)

This test is analogous to indirect (two steps) Coomb's test. Allergen (analogous to the RBC surface antigen) is coupled to insoluble polysaccharide substance (analogous to the RBC itself) to render the allergen insoluble. If specific reaginic antibodies are present, the addition of patient's serum will result in IgE-allergen reaction and will remain bound

after washing, in the second step, radiolabelled antiserum to human IgE is added and after overnight incubation, the complex is again washed, and it is counted in a gamma counter. This procedure is more advantageous than skin test because it is specific, the results are quantitative, no patient risk, not influenced by drugs and is able to be performed in infants and the elderly. The major disadvantages are it is expensive and few allergen polymers available (Yunginger and Gleich, 1975).

Drugs Used in the Treatment of Asthma

Sympathomimetic Amines and Related Compounds: Current Advances

Despite numerous reports that the most striking finding in severe asthmatic attack is mucus plugging, it seems that the use of bronchodilators, especially sympathomimetic amines, still play an important role in the management of acute asthmatic attack as well as maintenance therapy of the so-called 'chronic and stable asthma'.

The principal action of sympathomimetic drugs is to stimulate beta-adrenergic receptors in bronchial smooth muscles. Stimulation of beta receptors increases the activity of adenylcyclase, an enzyme that promotes the formation of cyclic 3′5′-adenosine monophosphate (cAMP) from ATP and results in bronchodilation.

In the last several years it is clear that beta-adrenoceptor comprises two groups: $beta_1$-adrenoceptors located in the myocardium [illegible] noceptors located in the bronc[illegible]mooth muscles. Activation of $beta_1$-adrenoceptors gives inotropic and chronotropic cardiac stimulation leading to tachycradia, palpitation and occasionally increased blood pressure. The bronchodilation is resulted when $beta_2$-adrenoceptor is stimulated.

The older agents such as epinephrine and ephedrine activate both $beta_1$ and $beta_2$ adrenoceptors. In the last decade several new sympathomimetic amines have been searched continuously to find the less effect on $beta_1$-adrenoceptors or in other word selective $beta_2$-activity (Avner, 1975; Tashkin, 1977; Reed, 1978). Isoprenaline (isoproterenol) is the first beta stimulant derived from the parent compound, adrenaline. Metaproterenol, terbutaline, salbutamol and fenoterol are the most important of numerous agents developed thereafter, and believed to have selective $beta_2$-activity.

Other advantages of the discoveries are the broader possibility of route of administration and the longer duration of action on bronchial musculatures. Isoproterenol, available in parenteral and inhalation forms, has a short onset of action but its duration of action is also short, because it is rapidly taken into cells and inactivated by catechol-o-methyl-transferase (COMT). By oral route, isoproterenol is inactivated by sulfatase in the intestine. The newer derivatives are not inactivated by COMT, so the duration of actions are longer than epinephrine and isoprenaline. Orciprenaline, terbutaline, salbuta-

...l and fenoterol a... ...activated by ...testinal sulfatase hence it could be administered orally (Reed, 1978).

The pharmacological properties of sympathomimetic amines are well summarized by Rebuck, as seen in Table 5.

Although most clinical trials were undergone in adult subjects, it seems that clinical advantages of newer beta adrenergic stimulants were also recorded in numerous investigations in pediatric age group as well. Some apparent controversial results, however, still exist and need further studies. Short review of beta-adrenergic stimulants will be presented below.

TABLE 5 : *Some pharmacological properties of sympathomimetic amines*

Agent	Route of administration	$Beta_1$ Activity	$Beta_2$ Activity	Duration of action
Adrenaline	A; NS; IM; SC	+++	+++	+
Ephedrine	O	+++	++	+
Isoprenaline	A, IV	±+	+++	++
Isoetharine	O	+	+++	++
Orciprenaline	A; NS; IM; IV; O	+	+++	+++
Salbutamol	A; NS; O	+	+++	++++
Terbutaline	A; O; SC	+	+++	++++

A = pressurized aerosol; NS = nebulizer solution; IM = intramuscular; IV = intravenous; O = oral; SC = subcutaneous.

Adapted from Rebuck, A.S.: Antiasthmatic drugs: I. Pathophysiological and clinical pharmacological aspects. Medical Progress 2 (2) : 71 (1975).

Adrenaline (Epinephrine)

This catecholamine used in the treatment of asthma has more or less equal alpha- and beta- activity (Flod, Franz and Galant, 1976). This leads some authors to exclude this agent as the drug of first choice in the management of acute asthmatic attack especially in adult patients.

Although epinephrine has a powerful bronchodilating effect, its duration of administration is subcutaneously, which absorbed slowly; but it can be used intramuscularly to give immediate but unfortunately short effect. Epinephrine is not effective orally, however in 1% solution it can be used by inhalation, though it is not a popular route of administration.

In severe asthmatic attacks not responsive to aerosol bronchodilator, subcutaneous administration of epinephrine is often helpful, possibly because of

delivery of the bronchodilator drug via the circulation to airways peripheral to occlusive mucus plug (Tashkin, 1977).

Ephedrine

This agent is the first bronchodilator effective orally. It has a mild $beta_2$-adrenergic stimulation, but its $beta_1$-activity is said to be more pronounced. It is relatively safe in children when used in usual dosage, although central nervous system stimulation may occur, similar to, but less than that of amphetamine (Weinberger, 1975). When theophylline was introduced as effective oral bronchodilator, many manufacturers made fixed combinations of ephedrine and theophylline. At first it was considered as a rational and effective combination, but later studies suggested that the combination has a synergistic toxicity included central nervous system and gastrointestinal disturbances without significant synergistic therapeutic effect. However, study of Reed, Sims and do Pico (1978) indicated that the combination of 25 mg of ephedrine and 130 mg of theophylline gave good result in adult subjects, without additional untoward reactions.

The introduction of newer orally active and more efficacious bronchodilators with fewer side reactions has made the use of ephedrine becomes increasingly unpopular, although Emirgil et al., (1977) found that ephedrine was only slightly inferior when compared with metaproterenol.

Isoproterenol

Chemically, isoproterenol is derived by substitution of 2 hydrogen ions at the end of the side chain by 2 methyl radicals. It readily became popular because of its rapid onset of action and longer duration of action than that of epinephrine. It is available in inhalation as well as intravenous form. Unfortunately it activates both $beta_1$ and $beta_2$-adrenergic receptors, so that it often causes undesirable side effects.

Parry, Martorano and Cotton (1976) have used intravenous isoproterenol in patients with life threatening asthma in addition to other medications commonly used in the treatment of status asthmaticus. Of 34 cases studied, all below 16 years of age, 27 responded well while the other seven were considered failed and needed mechanical ventilation. They concluded in their uncontrolled study that, at least, intravenous isoproterenol can significantly reduce the number of patients who would need mechanical ventilation.

Compared with newer inhaled sympathomimetics metaproterenol and salbutamol, Choo-Kang, Simpson and Grant (1969) found that isoproterenol has shorter duration of action and has more cardiac effect. Similar result was also reported by Roth, Wilson and Novey (1977).

Of particular interest is the study of Trautlein et al., (1976) who found that 29 per cent of 41 patients receiving isoproterenol were unresponsive to the drug

(they used term paradoxical bronchospasm). Although their work is still debatable partly due to incomplete technical detail, it still valuable to prove that this unresponsiveness to isoproterenol is not solely caused by isoproterenol abuse (Jenne and Chick, 1976) as described by previous authors (Speizer and Doll, 1968). Svedmyr, Larsson and Thiringer (1976), however, found that chronic use of isoproterenol infusion gave no resistance to the drug. the addition of terbutaline, either oral or inhalation, improved the bronchodilation effect and did not cause resistance to isoproterenol infusion. They concluded that the development of resistance in patients with severe asthmatic attacks as proved in accordance with the increased sale of isoproterenol inhalation, mostly because of other factors such as bronchial obstruction and mucosal edema, although true resistance may develop if the patient often takes large doses of inhalation.

Metaproterenol (Orciprenaline)

This is a resorcinol, not a catechol derivative. It has a longer duration of action and less cardiac effect than isoprenaline (Choo-Kang, Simpson and Grant, 1969; Roth et al., 1977). But Garra and associates (1977) found that nebulized isoproterenol and metaproterenol had similar cardiac effects.

Long term use of metaproterenol, either in inhalation form (Swarts et al., 1976) or oral (Hyde et al., 1976; Brandon, 1976; Sackner et al., 1977) indicated that this agent has a consistent effect after several months of usage and generally no tolerance developed. Mild unpleasant reactions, mainly tachycardia was not considered clinically important.

When added to children receiving around the clock dose of theophylline, oral metaproterenol produces significant improvement than with theophylline alone without causing increased side effect (Gallant, 1978).

Terbutaline

Terbutaline, N-tertiary butyl homologue of orciprenaline, is said twice potent on bronchial muscle as orciprenaline with less active on heart muscles. Available in oral, subcutaneous and inhalation forms, it also has longer duration of action than the parent compound.

Roth, Wilson and Novey (1977) found an earlier and higher peak of activity of terbutaline when compared with orciprenaline, while Goldgraber (1977) reported similar clinical effectiveness between terbutaline and salbutamol in adult patients.

Smith et al., (1977) have compared the clinical effect of subcutaneously injected terbutaline and epinephrine in adult patients with asthma. The result showed that both drugs were highly effective bronchodilator, as proved by spirometric measurements. Interstingly, that in a dose producing an equivalent degree of bronchodilation, epinephrine has a lesser cardiac effects in contrast to the common agreement that terbutaline has

selective $beta_2$-activity. More studies are needed to explain this controversy.

Recent long term study of Larsson, Svedmyr and Thiringer (1977) indicated that chronic use of terbutaline did not cause any 'resistance' toward beta adrenergic stimulants, as has been reported by the same group on chronic use of isoproterenol.

Pang and others (1977) administered subcutaneous terbutaline to 10 asthmatics, ranging in age from 2 to 13 years who had failed to respond to the administration of adrenaline and aminophylline. Almost all of these status asthmaticus patients showed gross clinical improvement. Only 1 patient seemed failed to respond with repeated injections of terbutaline. Minimal cardiac effects were noted, included changes in the ST-T wave and an increase of P wave amplitude which were noted in 3 patients. These side effects were quickly reversible. The dose of terbutaline in this study was 0.01 to 0.02 mg/kg body weight, to be repeated as necessary every 15 to 30 minutes with the same dose (up to 0.04 mg/kg) until clinical response was noted.

Salbutamol

This is the most important saligenin derivative. When given by inhalation this drug has a rapid and long lasting bronchodilating effect than by oral route, possibly because it is well absorbed by the intestine and rapidly excreted via urine, while the absorption after inhalation is very small (Avner, 1975).

Thompson and Friedman (1977) gave intramuscular salbutamol in the dose of 20 micrograms/kg body weight and found rapid clinical improvement; the maximum rise in PEFR of more than 20% occurred within 5 minutes. Side effects, included tachycardia and tremor were recorded. No arrhythmia was noted.

The effectiveness of salbutamol inhalation on the obtructive small airways had been studied by Rubin et al., (1977). On their adult patients, inhalation of 400 micrograms of salbutamol increased the dynamic compliance at respiratory frequency of breath per minute (Cdyn-60) significantly, indicating that salbutamol has a potent bronchodilating effect on the small airways as well as large airways as reported by previous authors.

The effectiveness of inhaled orciprenaline, and salbutamol are very similar, hence little choose between them. All have rapid onset of action, long duration of action and less cardiovascular effect than isoprenaline (Rebuck, 1975; Roth, Wilson and Novey, 1977; Goldgraber, 1977).

Fenoterol

Fenoterol, or Th 1165a, is other resorcinol derivative. As metaproterenol, and terbutaline, fenoterol has a selective effect on $beta_2$-adrenoceptor with less effect on $beta_1$-adrenoceptor. This drug was recently shown to be slightly more powerful bronchodilating effect than salbutamol, as reviewed by Gumei et al., (1976).

Comparing the effectiveness of oral fenoterol and ephedrine, Simi and Miller (1977) found that this agent was superior to ephedrine as far as spirometric measurement was concern. The only side effect are nervousness and tremor; the latter is a common side effect of all beta adrenergic stimulants, possibly because of its action on adrenergic receptors in skeletal muscles (Reed, 1978). These side effects tend to disappear on prolonged use. Pennock et al., (1977) found no such side effects when fenoterol was administered as aerosol.

Plummer (1978) also noted the superiority of fenoterol to ephedrine. But he also found that drug tolerance to fenoterol was detectable after 45 days of treatment and became more prominent after 90 days. Partial recovery in bronchodilating response appeared to occur after one week of therapy.

Theophylline

This xanthine derivative inhibits the degradation of cAMP to 5'AMP by competitive inhibition toward the enzyme phosphodiesterase, thus increases cAMP level that leads to bronchial dilation, and suppresses the release of mediators histamine, SRS-A and ECF-A (Goldberg et al., and Orange et al., as cited by Bierman, 1977). In spite of popular and long clinical use of theophylline, this agent still draws large attention of many authors. In current literature, one not argues about its effectiveness as a bronchodilator, but mainly to find out the rational dosage of theophylline, especially in pediatric age group.

It is strongly recommended that the therapeutic range of theophylline is between 10 to 20 micrograms/ml of serum; values below 10 will result in subtherapeutic effect, while concentration above 20 micrograms frequently associated with toxic symptoms. Due to its narrow margin of safety, many authors have investigated the optimal dose of theophylline in asthmatic children (Hyde and Floro, 1974; Ellis, Koysooko and Levy, 1976; Leung, Kalisker and Bell, 1977; Rangsithienchai and Newcomb, 1977; Walson, Strunk and Taussig, 1977). They found that the clearance rate of theophylline in children was far more rapid than in adults, so that children relatively require larger and more frequent dose to achieve therapeutic effect.

Certain conditions such as febrile illness (Rangsithienchai and Newcomb, 1977) and concurrent use of troleandomycin (Weinberger et al., 1977) inhibits theophylline clearance and produce higher serum theophylline level than expected.

In spite of common believe that phenobarbital acts as an enzyme inducer, that may enhance the biotransformation of many drugs used concomitantly. Piafsky, Sitar and Ogielvie (1977) reported that 14 days phenobarbital pretreatment did not alter theophylline disposition. On the other hand when phenobarbital pretreatment is given in a longer dura-

tion (28 days), theophylline clearance is increased, thus lower serum theophylline will result (Landay, Gonzales and Taylor, 1978). It may be concluded that short concurrent administration of phenobarbital needs no alteration of theophylline dose, while if phenobarbital is given for more than 2 weeks the dose of theophylline should be increased.

The difficulty to find optimal therapeutic dose of theophylline in children, as do in adults, is the fact that there are either interpatient (Rangsithienchai and Newcomb, 1977; Fixley, Shen and Azarnoff, 1977) or intrapatient (Walson, Strunk and Taussig, 1977) theophylline kinetics.

In contrast to Rangsithienchai and Newcomb who stated that repeated levels of serum theophylline on individual patient receiving the same dose of theophylline showed high degree of consistency. Walson, Strunk and Taussig found that repeated clearance value on individual patient may vary significantly. This controversial matter leads to doubt whether a single determination of theophylline kinetics in individual receiving theophylline will be of value in deciding the dose of theophylline for certain patient.

A study of Galant and associates (1977) indicated that there was a strongly positive correlation between plasma and salivary theophylline levels, so that salivary theophylline concentration may be used as a guide to plasma theophylline level. On the other hand Hendeles et al., (1977) found that salivary and plasma theophylline were not consistently well correlated.

At present time there is no reliable method to determine the optimal dose of theophylline for individual patient. Clinical individualization i.e. adjusting the dose to achieve clinical improvement while avoiding signs and symptoms of intoxication is still of practical use and may be warranted, especially in places where sophisticated laboratory examination is not available. The recommended dose in pediatric textbooks, 4 to 6 mg/kg body weight 4 times daily might be used as a guide. A full guide to oral theophylline therapy for the treatment of chronic asthma has been proposed by Hendeles, Weinberger and Wyatt (1978), this will be reviewed later (see treatment).

The form of theophylline used also needs consideration when prescribing the drug. In oral use, theophylline is better absorbed in a solution than solid form; the absorption also faster if it is given immediately after protein rich meal (Weilling et al., 1975). Fixley and co-workers (1977) had also found that oral preparation, an elixir form gave most rapid absorption. According to Mitenko and Ogilvie (1974), sustained released tablet can be used twice daily with favorable result. This method may be used in older children.

Systemic Steroids

Glucocorticoids have been extensively used in the management of status asthmaticus as well as maintenance therapy

of cases who can not be controlled by other measurements. Controlled study of the British Medical Research Council (1956) is considered to be the hallmark in the use of corticosteroids in the management of status asthmaticus. The study has proven that oral cortisone acetate gave beneficial effect in status asthmaticus.

However the exact clinical benefit of steroid is not without controversy. Pierson, Bierman and Kelley (1974), giving corticosteroids (hydrocortisone, dexamethasone or betamethasone) concomitantly with bronchodilators in patients with status asthmaticus, failed to demonstrate significant spirometric difference when compared with bronchodilators alone. The only significant difference was that in steroid treated patients the $Pa0_2$ levels were higher than in control group.

McFadden et al., (1976) also failed to find any spirometric improvement in patient with status asthmaticus treated by single dose of intravenous hydrocortisone, But Klaustermeyer and Hale (1976) in a single blind study observed spirometric improvement after intravenous administration of methylprednisolone. The study used 8 severely asthmatic adults who had failed to respond to a medical regimen of high dose bronchodilators, hyposensitization and environmental control, and had not previously treated with steroid except one. The earliest response to methylprednisolone occurred at 2 hours with peak response at 4 to 6 hours. Significant changes include both central and peripheral airways. No improvement was recorded when the same subjects were given saline solution. They concluded that methylprednisolone is useful in the management of status asthmaticus, but since the effect is delayed to 2 to 6 hours, the drug should be given early and in adequate dose.

Those controversies and other varied results reported in the literature lead Lecks (1977) to conclude that the responsiveness to steroid therapy in acute attacks depends upon the pharmacokinetic of the drug, target organ sensitivity, duration and severity of attack, previous medication prescribed especially steroids, age of the patient, genetic factors, the site of airway obstruction and the method utilized to assess pulmonary responsiveness.

Mechanism of action

The exact mechanism of action of steroid in asthma is not fully known. Some authorities (Rebuck, 1975) believed that steroid possibly inhibits IgE formation, while others (Claman, 1975; Hubscher, 1977) stated that corticosteroids do not influence the production of IgE. Settipane, Pudupakkam and McGowan (1978) found a decreased serum IgG and IgA with unchanged serum IgM concentration following steroid treatment. Serum IgE initially increased only when compared with other immunoglobulins and then decreased to pretreatment level after 22 days of steroid discontinuation.

The most obvious effect of steroid is its antiinflammatory activity, although

the precise mechanism is still in speculation. Stevenson (1977) hypothesized that this agent induces the release of peptide hormone from monocytes and other phagocytic cells, which in turn inhibits the formation of microfilament within the PMN, resulting in the inhibition of their margination, migration and lysosomal enzyme secretion. By this way, mucosal edema, bronchial and peribronchial cellular infiltration and bronchial secretion are depressed. This hypothesis probably can explain in detail what Claman (1975) has proposed, that antiinflammatory effect of steroid is through vasoconstriction, decreased chemotactic and interference with macrophages.

Furthermore Claman believed that corticosteroid has a major role in the inhibition of types I, III and IV immunologic injury.

Whether or not steroids increase the cAMP level is still in doubt (Rebuck, 1975; Claman, 1975; Lecks, 1977). But it seems clear that antiinflammatory effect of corticosteroid has a greater therapeutic significance than its spasmolytic effect.

Untoward reactions

The most undesired side effect of steroid treatment in children is stunted growth (Drug Committee, 1967; Shapiro, et al., 1977) This phenomenon is caused by suppression of the growth hormone secretion (Hartog, Gaafar and Fraser, 1964), as a consequence of so-called adrenal-pituitary axis inhibition (Falliers et al., 1972). Not less than 20 other side effects of prolonged steroid administration have listed by the Drug Committee of the American Academy of Allergy (1967) including weight gain, moon faces, ecchymoses, hirsutism and osteoporosis. The Committee also noted a higher rate of side effects if the treatment is given for more than 2 years. In the contrary, Lieberman, Patterson and Kunsker (1972), evaluating adult subjects, found that the frequency of side effects were not correlated with the duration of treatment, but increased with increasing of the patient's age.

Rimsza (1978) has classified the steroid complications into ophthalmologic, CNS, hematopoetic system, gastrointestinal system, renal system, musculoskeletal system, metabolic and endocrine systems.

Shapiro et al., (1977) reported that steroid dependent asthmatic children obviously showed growth suppression and retarded bone age; the same complications were also observed in less frequency in non steroid dependent asthmatics. Plasma 17-OH-CS in non steroid dependent group was abnormal in 42% of cases, while in steroid dependent was 55%. This data support the earlier hypothesis that asthma alone is able to cause adrenal-pituitary axis suppression.

To reduce such effects, attemps have been made by giving concomitant or intermittent ACTH, anabolic steroids and somatotrophic hormone; but the most widely accepted method is the alternate-day regimen. Klaustermeyer and Hale

(1976) studied 6 asthmatic adults using daily [illegible] by alternate-day steroid. After 10 days of daily treatment, improvement of respiratory function was observed, and further improvement was noted with 3 weeks of alternate day treatment. In children, Falliers et al., (1972) reported that pulmonary function of those receiving alternate day steroid can be maintained at satisfactory level throughout 48 hours, while plasma cortisol level showed normal circadian rhythm. There are evidences that alternate day therapy reduce the incidence of side effects (Dujovne and Azarnoff, 1975). With this mode of treatment, the total dose should be given single in the morning every other day.

Aerosol Steroids

In spite of excellent results on the control of asthma by the use of sympathomimetics and cromolyn sodium, there are still a considerable number of patients who could not be managed and need prolonged use of corticosteroid. The side effects of systemic steroid therapy are wellknown (supra). Newer steroid preparations such as triamcinolone or betamethasone seem do not decrease the reported side effects, nor does intermittent use of corticotrophin. Alternate day regimen, although offers some advantages, does not eliminate all of the side effects.

To overcome this problem, extensive research has been done, and the answer, at least in part, has been found with the introduction of aerosolized steroid. The most important compound is beclomethasone diproprionate.

Trials with beclomethasone inhalation have been reported elsewhere. Bulow and Kalen (1974) studied adult patients with steroid dependent asthma. Of 27 patients evaluated, 19 were able to wean oral steroid (excellent result), 7 were good responders and the other 1 did not respond at all. Similar result was also reported by Hodson et al., (1974) and Vogt et al., (1976), as measured by objective pulmonary function testing as well as subjective feelings by the patients. When the drug was used in long term setting, Spitzer et al., (1976) found that beclomethasone aerosol has a consistent effect in most of the patient studied.

In the pediatric age group, many authorities noted excellent results both on short term (Dickson et al., 1973; Godfrey and Konig, 1973; Lovera et al., 1977) and long term (Godfrey and Konig, 1974) studies as seen in Table 6.

Dosage

The dose of beclomethasone diproprionate is adjusted to the response, varied from 100 micrograms (2 puffs) to 800 micrograms (16 puffs) per day. Most children could be controlled by 400 micrograms (8 puffs) daily, divided in 3 to 4 doses (Godfrey, 1975). Toogood et al., (1977) demonstrated that high dosage of beclomethasone gave more accurate result than low dosage.

After administered by aerosol, the majority of the drug is swallowed and absorbed by the gastrointestinal tract.

TABLE 6 : *Overall results of clinical trials using beclomethasone inhalation in asthmatic children*

Authors	No. of patients	Age range	Duration of treatment	Good to excellent result
Dickson et al. (1973)	25	5 — 16 yrs	10 — 28 weeks	17 (68%)
Godfrey & Konig (1973)	20	6 — 20 yrs	12 weeks	19 (95%)
Godfrey & Konig (1974)	26	5 — 15 yrs	13 — 20 mo	25 (96%)
Lovera et al. (1977)	42	4 — 15 yrs	3 — 6 mo	36 (86%)

Because of its potent topical action the small amount reacting the lungs can control the asthma, while the absorbed portion is insufficient to suppress the adrenal glands.

Side effects

The most important advantage of aerosol steroids is that the drug is able to replace systemic steroids without any significant systemic side effects. Both in adult (Spitzer et al., 1976; Bulow and Kalen, 1974; Vogt et al., 1976; Davies et al., 1977) and in children (Godfrey and Konig, 1973; Dickson et al., 1973; Godfrey and Konig, 1974; Lovera et al., 1977), beclomethasone did not suppress the adrenal function in contrast to systemically administered corticosteroid, as analyzed by serum or urine or both.

Reported side effects of beclomethasone included oral and pharyngeal moniliasis especially in adults and exacerbation of eczema or rhinitis in patients previously treated with systemic steroid (Godfrey and Konig, 1974). Horton and Spector (1977) reported an adult patient who developed pulmonary tuberculosis while taking beclomethasone.

Other aerosolized steroids

Several other topically active steroids have been investigated to control asthma. Limited data concerning the effectiveness of such agents are available included the use of betamethasone valerate in adults (Hartley, Charles and Seaton, 1977; McAllen, Kochanowski and Shaw, 1974) as well as in children (Frears, Wilson and Friedman, 1973; Hiller and Milner, 1975).

Williams, Kane and Shim (1974) studied the clinical effect of triamcinolone acetonide delivered by aerosol. All investigators noted some beneficial effects with little or no side effect.

Indication

Although it seems that beclomethasone is very effective and without serious

side effect, considering that this drug is relatively new, it is not recommended to be used unless other measurements have failed to control asthma. Godfrey (1975) recommended the following guidelines in the use of aerosolized steroids :

1. Children who can not be controlled on cromolyn or bronchodiators without restoring to systemic steroid;
2. Children already on steroid who can not be weaned from them to cromolyn or bronchodilators.

In addition, due to technical reasons it is difficult to administer inhaled steroids to infants and very small children.

Disodium Cromoglycate

This compound, also known as cromolyn sodium, is a bis-chromone, a synthetic analogue of khellin, a botanical extract of Ami visnaga, which was known since ancient times as a smooth muscle relaxing agent of little practical use due to its side effects (Falliers, 1975).

Developed by Dr. Altounyan, cromolyn sodium is quite a unique compound; it is not related to any of previously agents used in the treatment of asthma such as sympathomimetics, antihistamines, xanthines and corticosteroids.

It has neither bronchodilating nor anti-inflammatory effect, it also does not prevent antigen-antibody interaction. The most probable mode of action of cromolyn is to stabilize the cell membrane through interference with calcium transport with the consequence of preventing chemical mediators release. Consistent to this postulate, cromolyn can only be used as a prevention of asthmatic attack, but not as a treatment of acute asthma.

Since cromolyn is poorly absorbed by the intestine, it must be administered by inhalation. A dry powder of this drug is contained in gelatin capsule. The capsule is punctured by movement of two concentric pins of an inhaler, and then with deep inspiration the flow of air enables it to spin and release the micronized drug flow into the lungs. Three to six inhalations usually empty the capsule. If it is done properly, about 10% reaches the lungs, while the remainder being deposited in the mouth and pharynx and then swallowed into the gastrointestinal tract.

Many studies on the effect of disodium cromoglycate have been reported. Mascia, Friedman and Kornfield (1976) reported their long term efficacy of cromolyn in 53 asthmatic children. They observed that the agent proved to be highly effective as indicated by the improvement of asthmatic symptoms, i.e. wheezing, coughing, sleep disturbance and amount of sputum as well as the reduction of exercise handicap. The amount of antiasthmatic agents previously used i.e. bronchodilator, aerosolized adrenergic and corticosteroid were significantly reduced. Study of Hermance and Brown (1976) on 21 subjects ranging in age from 7 to 60 years gave similar result, but they found the gradual decrease in the effectiveness of the drug in long term use in some patients. This

most likely due to the more severe asthma during the course of the disease, causing cromolyn less effective. Increasing the daily dose may counteract this phenomenon, and reuse after several months worn of gave good result.

With limited number of patients, Matondang-Siahaan and Bratawijaya (1977) found that extrinsic asthmatic children who showed deformity of the chest i.e. barrel-shaped chest which may reflect the chronicity of the disease, responded less to cromolyn sodium; the drug effect was impressive in patients without such deformity.

Dalayeun, (1973) noted 77% success rate with cromolyn sodium, while the other 20 and 3% showed moderate and no response, respectively. In a small study using cromolyn and beclomethasone diproprionate, Mitchell and others (1976) failed to demonstrate that the combination was superior in controlling asthma compared if either drug was used singly. Large studies are needed before making such disappointing conclusion remembering that the two drugs have different mode of action.

Irani et al., (1972) found that cromolyn sodium was effective in both extrinsic and intrinsic asthma, but in extrinsic asthma the effect was more pronounced. Cromolyn is also able to prevent exercise-induced asthma, superior to that of inhaled ipratropium bromide (Chan-Yeung, 1977).

Although some other allergic conditions respond well to cromolyn such as ulcerative colitis (Mani et al., 1976) and allergic rhinitis (reviewed by Falliers, 1975), the principal indication of this agent is bronchial asthma. Flod, Franz and Galant (1976) recommended the following asthmatic subjects who may receive cromolyn therapy :

1. Asthmatic patients who could not be controlled by appropriate doses of theophylline or sympathomimetic amines;
2. Steroid dependent asthma, hoping that the dose of systemic corticosteroid will be reduced if not eliminated;
3. Exercise-induced asthmatics who are not easily controlled by standard bronchodilators;
4. Patients who have been proved to be severely sensitive to specific airborne allergens.

All patients receiving cromolyn should use bronchodilator, especially when they are wheezing. If wheeze appears, cromolyn should be discontinued, and a sufficient dose of efficacious bronchodilator is instituted. When the patient is steroid dependent, he must receive suitable steroid; it also should be given when a stressful situation arises.

Cromolyn is a safe drug, although some hypersensitivity phenomena have been noted. No teratogenic effect has been found in animal study, and expecting mothers taking cromolyn are known to have given healthy infants.

Using face mask, nebulizer and specifically designed compressor instead of

conventional spinhaler, Marks (1977) succeeded to administer cromolyn sodium in asthmatic children as young as 16 months with no significant difficult.

Current Status of Immunotherapy in Childhood Asthma

Pros and cons in the field of medicine is quite common. It is particularly true in the case of immunotherapy in asthma. On the one hand May (1975) did not believe that immunotherapy will give benefit to most cases with asthma. On the other hand, experts like Collins-Williams (1977) beat those who criticise the value of immunotherapy and stated that such procedure, when performed in a proper manner with proper materials will give benefit in the majority of cases. Good result can be expected in excess of 90% (Nizami and Collins-Williams, 1975). Johnstone (1968) found that about three quarter of asthmatic children will resolve its clinical symptoms with immunotherapy, while those who did not receive immunotherapy only 22% outgrew the disease by the age of 16 years. This controversy seems will continue until further well conducted studies and better method of evaluation give sufficient data to make more or less uniform conclusions.

The practise of giving injections of allergen extracts to treat allergic disorders has been done as early as 1911, before adequate studies and sufficient control trials were available. Later opinion proposed that asthma, an extremely complex disease with bronchial hyperreactivity as a basic pathology, may be altered by giving repeated injections of allergens in increasing doses over long period of time. It is considered to have a rational basis when the precipitating factor is an extrinsic allergen. In childhood asthma this is the case, because nearly 95% of asthmatic children are of extrinsic type.

Until recently, the efficacy of immunotherapy in asthma could be evaluated by clinical observation only. The most frequent parameters used are decreased severity of asthma attacks, decrease duration of wheezing or number of years attacks occur. If these criteria will be rigidly followed, it is very difficult to reach a conclusion that such procedure is effective or ineffective in treating asthma. First of all, due to its long provement reported of ter several years of immunotherapy is the result of the treatment or it is by itself the natural history of the disease. Other important factor is the lack of standardization of allergen extracts used. This may best illustrated by a study of Gaddie et al., (1976) which reported the value of hyposensitization therapy with commercially available house dust mite vaccine in bronchial asthma for 12 months. This group did not observe any improvement in symptom score, spirometry, skin and nasal challenge when compared with control group. The possible cause of this failure was the low strength of allergen extracts they used. Several authors who used 3 times stronger than the commercially available extract found the good result.

May (1975) reviewed that reports on hyposensitization therapy in the last 10 years showed these characteristics : (1) most studies were done on allergic rhinitis, few on asthma; (2) each study used limited number of allergens and few subjects; (3) some of the study used scoring system which is depended on the subjective symptoms; (4) other drugs were given both to treated and control subjects; (5) the test of effectiveness depended on natural seasonal exposure.

Collins-Williams (1977) pointed out that immunotherapy is an immunologic procedure, hence the best parameters to evaluate its result should be the immunologic ones. He objected the criticism that the value of immunotherapy in asthma is unproven simply because many published reports have not been desprove its efficacy. Those immunologic parameters, which have been described by Irons et al., (1975) and Evans et al., (1976) are now considered as the mechanism of action of immunotherapy.

(1) After several injections of specific allergen extract, there is an elevation of specific antibody (IgG). This immunoglobulin is called as 'blocking antibody' which combines with specific allergen so that it blocks allergen from combining with mast cells, thus the liberation of mediators of anaphylaxis is prevented. It should be emphasized that this blocking antibody is specific to the injected allergen.

(2) It has been demonstrated in vitro that following injection therapy, the amount of histamine that will be released by the basophils after exposure with allergen is greatly reduced. Since the mast cell is similar to basophil in the blood, it is presumed that the same thing happens to the mast cells. Flod, Franz and Galant (1976) called this phenomenon as to change in cell sensitivity.

(3) After several years of immunotherapy, the production of specific IgE decreases. The may be the most important factor, and thought as due to IgG feedback or T-cell tolerance that interferes with T-cell - B-cell interaction which is necessary for IgE production. However, until now it has not been demonstrated that low serum IgE means low IgE attached to the basophils and mast cells (Collins-Williams, 1977).

In addition, Norman (1978) believed that after immunotherapy several measures of lymphocyte function in the presence of specific antigen are reduced.

It should be emphasized that when good result is expected, correct diagnosis and detection of specific allergen should be established, usually by skin testing. Taylor, Ohman and Lowell (1978) demonstrated good result in patient allergic to cat pelt extract. After 3 to 4 months receiving weekly or biweekly injections, treated subjects showed a significant mean reduction in both skin and bronchial reactivity to cat pelt extract. This study showed that if specific allergen is detected, then special immunization will be of value.

Failure to obtain favorable result might be due to : (1) uncorrect diagnosis; (2) failure to detect specific allergen; (3) too weak or too strong allergen extract; (4) too long interval of injections; (5) failure to obtain environmental control and other general measurement including food allergen avoidance as well as emotional and physical stress.

Czarny (1976) pointed out that if better result is to be obtained, the following 'ten commandments' must be followed :

(1) The patient must be atopic
(2) The relevance of allergen must be determined
(3) The allergen is unavoidable
(4) The allergen must induce significant disease
(5) Examine the index of danger : those who need hyposensitization most, can tolerate it least
(6) Specific extract, ideally single allergen must be used
(7) Tailored and individualized dosage schedule
(8) Reliable source of administration
(9) Adequate and continuous review
(10) Adequate total cumulative dose must be used.

Immunotherapy, has been performed using inhalants, house dust, pollens, animal danders etc. Hyposensitization against food allergy is usually not indicated, since it can be avoided easily (Tuft, 1973).

Managemet of Asthmatic Children

Treatment of acute attack

In acute asthma, adrenergic agents are the drug of choice. Subcuataneous injection of epinephrine hydrochloride (1 : 1000) aquaeous in a dose of 0.01 mg/kg body weight is often helpful. If necessary the injection may be repeated up to 3 times with interval of 10 to 20 minutes. Bierman (1978) stated that isoproterenol inhalation 0.05% given in 10 minutes with oxygen by nebulizer may replace epinephrine; it may also be repeated up to 3 times Clinical monitoring before, during and after initial treatment is mandatory. If improvement occurs after adrenergic stimulant administration, theophylline should be instituted 4-6 mg/kg every 6 hours, but it can be preceded by the administration of epinephrine suspension (susphrine) 0.005 ml/kg subcutaneously with maximum dose of 0.15 ml. If such procedures fail to give any improvement, then the child should be hospitalized and to be managed as status asthmaticus.

Status Asthmaticus

Status asthmaticus is that state of severe asthmatic attack which fail to respond readily to the usual methods of therapy, particularly epinephrine (Richard and Siegel, 1969). Although some physicians reluctant to use this term (Clark, 1977), most authorities believe that it still of practical use. Parry, Martorano and Cotton (1976), and Pierson, Bierman and Kelley (1974) needed 3

subcutaneous epinephrine injections in adequate doses given at 15 to 20 minutes interval before diagnosing status asthmaticus.

Factors that may cause refractoriness to epinephrine are poorly understood, but the following features are said to have a role in the pathophysiology of status asthmaticus :

(1) infection which is frequently found in children with status;
(2) failure to give large doses of corticosteroids;
(3) dehydration leading to formation of mucus plugs;
(4) sedation and narcotics;
(5) excessive use of nebulizer epinephrine or isoproterenol;
(6) epinephrine-histamin homeostasis balance upset;
(7) acidosis;
(8) hypoxemia.

Management

1) Evaluation of laboratory changes

Complete blood examination, urinalysis, tuberculin tests as well as electrolyte determination should be performed. Electrocardiogram should also be obtained if there is a doubt in cardiac status. But the most important and urgent examination in every child with status asthmaticus is the determination of acid base balance and blood gas analysis. Measurement of pH, arterial PO_2 and PCO_2 and acid base excess may be required as often as every 20 minutes depending upon the trend of previous measurement.

Hypoxemia is invariably present in asthmatic attack. Early during attack, hypocarbia is present secondary to hyperventilation (McFadden et al., 1973; Levison et al., 1974). As the attack progresses, the arterial PCO_2 will rise indicating diminished alveolar ventilation.

Acidosis is another consistent finding in status asthmaticus, which is of 2 types : metabolic acidosis as the consequence of fever, poor intake leading to dehydration, increase in work of breathing and the lack of oxygen causing anaerobic metabolism, and respiratory acidosis due to the failure of the lung to eliminate CO_2.

2) Medical therapy

Medical management is still considered as the basic treatment of status asthmaticus, and it works in the majority of cases.

Hydration. Intravenous administration of fluid with electrolyte (usually 5% glucose in 0.25 normal saline is sufficient) is mandatory to correct or to prevent dehydration which might cause inspissation of mucus in the bronchial tree (Richards and Siegel, 1969). Cotton and Parry (1975) recommended to give 2½ times maintenance.

Oxygenation. Start to give oxygen by nasal canula, nasal catheter or mask at least 2 liters/minute to keep the arterial PO_2 65 mmHg or more. Oxygen should be humidified to avoid its drying effect and should be given continuously rather than intermittentlyy. Cyanosis can not be use as a sign of hypoxemia, since it usually can not be detected until the PO_2 falls to 50 mmHg. Hence, arterial blood

gas analysis is the only reliable guide to detect early hypoxemia.

Alkalinization. Sodium bicarbonate or THAM should be administered early to combat acidosis. The amount of milliequivalent required is 0.3 × body weight (kg) × base deficit. Some authors prefer to give half of the calculated dose in a bolus and the remaining half within the subsequent hours, while the others recommend to give the total dose slowly over a period of 1 hour. Since patients suffering from acute respiratory acidosis may have a normal base excess, Richards and Siegel (1969) used Kaplan's formula for calculating milliequivalent of alkalinizing agents : 1.5 × body weight per hour. Further administration depends on the state of acid base balance.

Theophylline. Every child with status asthmaticus should receive intravenous theophylline 4-6 mg/kg body weight every 4 to 6 hours, run rapidly over 30 minutes. The daily dose theophylline should not exceed 36 mg/kg body weight.

Sympathomimetics. By definition, a patient with status asthmaticus is refractory to epinephrine consequently it should not be used to treat status, otherwise toxicity will develop. Parry, Martorano and Cotton (1976) succeeded to treat 27 out of 34 children with status asthmaticus with intravenous isoproterenol. Subcutaneous terbutaline (0.01 to 0.04 mg/kg) given every 15 to 30 minutes if necessary has been reported to be effective in the treatment of status asthmaticus (Pang et al.. 1977).

Corticosteroids. Regardless previous treatment received, patient with status asthmaticus should be treated with large doses of corticosteroid (100 to 200 of hydrocortisone or equivalent); of needed the dose may be repeated every 4 to 6 hours. Pierson, Bierman and Kelley (1974) have found that the administration of corticosteroid will significantly increase PaO_2 level, although it was not accompained with spirometric improvement when compared with control group.

If steroid is given for less than 5 days, it can be stopped obruptly, gradual reduction is not needed.

3) Mechanical ventilation

Mechanical ventilation may be needed in patient with status asthmaticus who develops respiratory failure. The most widely accepted criteria of respiratory failure is that of Downes, Fulgencio and Raphaely (1972), which needs 3 clinical and 1 physiological criteria (see Table 7).

TABLE 7 : *Criteria for respiratory failure in infants and children with acute pulmonary disease.*

Clinical	: Decreased or absent inspiratory breath sounds Severe inspiratory retractions and use of accessory musles Cyanosis in 40 per cent ambient oxygen Depressed level of consciousness and response to pain Poor skeletal muscle tone.
Physiologic	: PCO_2 more than 75 mmHg.PO_2 less than 100 mmHg in 100 per cent oxygen.

After Downes, Fulgencio and Raphaely : Acute respiratory failure in infants and children. Pediat. Clin. N. Amer. 19 : 423 (1972).

These criteria are not rigidly followed by some authorities, who found in their experiences that some patients with $PaCO_2$ above 75 mmHg who have not received optimal treatment could be reversed with medical therapy alone, while other patients who have been treated adequately with $PaCO_2$ in the 30's will need mechanical ventilation (Cotton and Parry, 1975).

Mechanical ventilation is done with volume cycled respirator which is able to deliver large inspiratory pressure of 80 to 100 mm of water. The patient is intubated, either through orotracheal or nasotracheal route.Grislain et al., (1973) recommended that mechanical ventilation should not exceed 36 hours.

This procedure, although effective in treating severe status asthmaticus is not without complications. Minor complications of intubation, pulmonary atelectasis, pneumomediastinum and subcutaneous emphysema, pneumothorax, pulmonary infection, cardiac arrhythmia and metabolic alkalosis have been reported (Simons, Pierson and Bierman, 1977). It should be emphasized that too rapid in the reduction of $PaCO_2$ may cause sudden death, possibly through cardiac arrhythmia. For these reasons, mechanical ventilation should be carried out by experienced hand in well equipped and well staffed centers.

Management of chronic asthma

Avoidance

Avoidance to the causative allergens is the ideal procedure in the management of extrinsic asthma, but in fact this is extremely difficult to conduct. It is impossible, for instance, to avoid breathing pollens in the air. But some allergens in the home, especially house dust can be minimized if not totally eliminated. Since a child spends most of his indoor life in his bedroom, this place should be the major area for house dust control (Flod, Franz and Gallant, 1976).

In the industrial countries where socioeconomic factor is not a major problem and good housing is usually available, an almost complete house dust free bedroom is possible to obtain. The use of humidifier, electronic filters and air conditioner (Ghory, 1977) is of great value in reducing house dust.

Avoidance of food allergens may be difficult to obtain, but it can be tried with hypoallergic diet, especially in baby food (Ford, 1976). Avoiding too early ingestion of potent allergenic protein such as cow's milk and egg white may be justified in a baby with strong family history of allergy, and breast feeding should be given as long as possible.

Obviously other factors than allergens that may induce bronchoconstriction such as prolonged exercise, rapid change in climate and irritants included smoking or smoke fog should be avoided.

Psychological care

Although asthma has been known since long time as an example of psychosomatic disease, the exact prevalence of

emotional disorder in asthmatic children is not known. It is believed that psychological stress might induce bronchoconstriction in certain asthmatic children; however, there is evidence that no certain childhood personality traits predispose to asthma, and no individual or family conflicts uniformly and consistently are associated with asthmatic attacks (Mattson, 1975). Home environment is important in psychological aspects of asthma; some children will have rapid remission of their symptoms when hospitalized or away from home, even with unchanged therapeutic regimen.

A general approach should be carried out to give the favorable emotional feeling to asthmatic children. Love and affection, security, acceptance as an individual, self respect and achievement, avoiding the sense of dependence and to establish self discipline are amongst the factors that should be carefully considered (Ghory, 1977). It is the physician's responsibility to explain such matters to the parents.

To adolescent asthmatics, open group discussion with competent physicians, psychiatrists, social workers and elders may give benefit in giving better understanding on their disease (Tinkelman et al., 1976).

Immunotherapy

Albeit there's still debate on the value of hyposensitization therapy as reviewed earlier, the benefit of such procedure may be reasonably expected, particularly for asthma caused by pollens and house dust mite with strong skin sensitivity (Ford, 1976). Immunotherapy should be tried in asthmatic children who are sensitive to inhalants, based on clinical history and skin test. It is a long procedure and needs the cooperation of the physician, patient and parents. The dosage of allergen extract should be the highest concentration tolerated.

Pharmacology

Theophylline is the drug of first choice in the maintenance treatment of chronic asthma. It should be given in the initial dose of 4 mg/kg body weight every 6 hours with maximal dose 400 mg/day. If necessary increase the dose in approximately 25% increments at 3 day intervals. If possible plasma theophylline concentration should be measured and the dose of theophylline to be adjusted to give plasma through concentration of 10 to 20 micrograms/ml. If plasma theophylline measurement is not available, the dose should not exceed the following: age less than 9 years: 24 mg/kg/day; age 9 - 12 years: 20 mg/kg/day; age 12 - 16 years: 18 mg/kg/day; age more than 16 years : 13 mg/kg/day or 900 mg/day (Hendeles, Weinberger and Wyatt, 1978).

Many authorities recommend to give oral adrenergic stimulants to supplement theophylline. The most frequent agent prescribed is metaproterenol, which replaces the older oral adrenergic bronchodilator, ephedrine. The initial dose of metaproterenol is 2 mg/kg/day in six divided doses. If necessary it is gradually

increased until the asthma is controlled (Bierman, 1978). In some instances concurrent administration of metaproterenol may reduce theophylline dosage.

Other oral sympathomimetics such as terbutaline and fenoterol are of limited use in pediatric age group. But terbutaline may be given orally in children above 12 years with the dose of 2.5 to 5 mg every 6 hours.

Cromolyn sodium may prevent asthmatic attack if a 20 mg capsule is inhaled 4 times daily, regardless the patient's age. The indication of using cromolyn has been described earlier.

Costicosteroid is used only when theophylline, adrenergic agent and cromolyn sodium fail to control the symptoms. In acute asthma, short course of prednisone (1 - 2 mg/kg/day) may be effective; as the attack reliefs, it should be reduced 5 mg/day until it is discontinued. If long term steroid is needed, the smallest dose which stabilizes lung function should be prescribed, and attempt to change into every other day regimen should be done as early as possible. Beclomethasone diproprionate, 2 inhalations three times a day should be tried; if this is effective, then the systemic steroid can be tapered. Complete description of aerosolized steroid has been reviewed.

Prognosis

It is difficult to point out precisely the prognosis of childhood asthma if one needs detail informations. The only exact fact is, based on many reports, that death from asthma is extremely rare, possibly not exceeds 1% after 20 years follow up.

Asthma is a chronic disease with wide spectrum etiologic and risk factors, so the outcome of the disease is widely influenced by such factors. There were many follow up studies on the natural history of asthma in children, but it is quite difficult to adopt certain conclusions from them because of these factors: (1) Each author or group of authors used different criteria, parameters and method of evaluation, (2) Most of them reported the result of retrospective study, not infrequently after losing the patients for many years, almost none have made prospective study, (3) Detailed therapeutic regimen given to the subjects studied is essentially lacking, so it is impossible to know a correlation between treatment and outcome of the disease except for few reports on hyposensitization, (4) Many reports based solely on questionnaire which open to the occurrance of bias, and (5) The results are not infrequently controversial.

Some risk factors that may influence the prognosis of asthmatic children will be reviewed below, and depicted on Table 8.

a. Sex. Male to female ratio is approximately 2 to 1 in children with asthma. By the time they reach adolescence, more boys are improving than girls (Rackemann and Edwards, 1952; Smith, 1961; Barr and Logan, 1964). But other authors (Johnstone, 1968; Blair, 1977) did not confirm this statement.

b. Age of onset. An early age onset is characteristic in childhood asthma, being as high as 57% under 2 years of age (Blair, 1977), Several authors examined the effect of early onset with the prognosis of asthma. Buffum and Settipane (1966) found that onset of asthma before 2 years of age was associated with continued or intractable course of the disease. This finding was confirmed by Williams and McNicol (1975), but Barr and Logan (1964), Johnstone (1968) and Blair (1977) found no significant correlation between age of onset and the long term prognosis. On the contrary, Rackemann and Edwards (1952) and Smith (1961) reported a more favorable prognosis in early onset asthmatics.

c. Breast feeding. Blair (1977) pointed out that early prognosis benefitting from breast feeding up to one week, but for long term prognostic improvement, breast feeding for more than 8 weeks was necessary. Wittig et al., (1978) found that breast fed infants had later age of onset than bottle fed infants.

TABLE 8 : *Factors that may influence the Prognosis of Childhood asthma according to several authors.*

Authors	Sex	Age of onset	Breast feeding	Family history	Associated Atopic Disease
Rackemann & Edwards (1952)	Yes	Yes*	N E	N E	N E
Smith (1961)	Yes	Yes*	N E	N E	N E
Barr & Logan (1964)	Yes	No	N E	N E	Yes
Buffum & Settipane (1966)	N E	Yes**	N E	N E	Yes
Johnstone (1968	No	No	N E	N E	Yes
Williams & Mc Nicol (1975)	N E	Yes**	N E	N E	N E
Blair (1977)	No	No	Yes	Yes	Yes

* earlier onset improves prognosis; ** earlier onset worsens prognosis;
N E = not examined.

d. Family history. Short term and long term prognosis are affected significantly by positivie family history of atopic disease in first degree family (Blair, 1977). Wittig et al., (1978) noted that bilateral family history of allergy correlate with the earlier onset of the disease.
e. Associated atopic disease. History of the concurrent of infantile eczema indicated bad prognostic sign (Barr and Logan, 1964; Johnstone, 1968; Blair, 1977). Other atopic disease i.e. allergic rhinitis also gave similar effect.

Furthermore, there is a good agreement among most authors that most of the remission occur in the second decade of life, and those who did not 'outgrow' the disease in their teenth would have less chance to have symptoms free. It also seems that the longer the follow up, the more patients will improve.

Comment

Despite certain controversies on many aspects of asthma, it is obvious that broad advances have been achieved, especially within the last 15 years. The disease, which has been known since Hippocrates times as early as 4 hundred years BC, has drawn continuous attention and efforts in practically all races and culture, since it does not have certain racial preponderance. The works and experiences of experts and physicians both before and after renaissance have valuable contribution in understanding the disease. But undoubtedly it was a slow and long process. If we consider that modern medicine began around the middle of the last century, we will also learn that the same impression will be found almost in half of that era.

With the introduction of the concept of allergy in the beginning of this century, then followed by the discovery of bronchodilators, the speed of the investigation of asthma became markedly increased. But the major breakthrough is the finding of the Ishizakas (1975) no the newly described immunoglobulin, then known as immunoglobulin E (IgE), which was previously hypothesized as reaginic antibody, the 'messenger' of allergic disorder. With this finding, many aspects of asthma, especially its pathogenesis, could be explained in a greater detail.

In the field of treatment, three major drugs have been discovered. First is the discovery of newer sympathomimetic amines, derived primarily from the parent compound, epinephrine. The advantages of these new adrenergic stimulants have been reviewed earlier. It seems that in this era, where excellent laboratory and qualified experts are easily available, further discoveries could rationally be expected continuously, to find the most selective $beta_2$ activity, longer duration of action with less untoward reactions.

Secondly, the introduction of disodium cromoglycate, an exceptionally unique agent that have been proven to be effective in preventing asthmatic attack in the majority of patients studied. Unfortunately, the

agent is too expensive to be used by most patients, especially in developing countries where health expenditure is remarkably low. If this disadvantage can be eliminated, undoubtedly Dr. Altounyan's purpose to help asthmatic patients will have been fulfilled.

The third important drug discovered is topically active corticosteroids. This aerosolized steroids may replace most cases of asthmatics who are steroid dependent, and it also may prevent the development of steroid dependent asthma, hence serious side effects of systemic steroids could be avoided while at the same time their therapeutic effect is maintained.

It also became readily available in clinical practice, but its high cost is still became as the obstacle in the wide usage of this excellent agent.

Advances in this antiasthmatic agents, together with the help of well equipped intensive care units, certainly has made a better control of asthma which in turn prevent many deaths from asthma. But these advances are mainly, if not merely, symptomatic. A big question still arises: whether the natural history of asthma could be altered by recent knowledge in asthma. In other word, whether the disease could 'cured' much more earlier.

At present time, the only possible an swer for that question rest with immunotherapy. In spite of many disadvantages in immunotherapy as reviewed earlier, at least there are certain significant figures indicating the benefit of injection therapy, e.g. report of Johnstone (1968) which noted that about 75% of treated children have 'outgrown' the symptoms while only a quarter of non-treated patients have symptom free by the age of mid-teenth.

The major obstacle in evaluating this kind of treatment is the fact that it is impossible to arrange a double blind — matched control study, mainly due to the natural history of the disease itself. Needless to say, we need further studies on this special matter, though it is unrealistic to expect definite conclusions in the near future, because immunotherapy needs long follow up study before it could be evaluated.

In conclusion, bulk of data indicate that asthma is a complex disease. It has immunologic and non-immunologic aspects, sometimes the border of the two is unclear. Consequently, the overall management of asthma in children should have an interdisciplinary approach, which involves the pediatrician, allergist-immunologist, physiologist, psychologist, psychiatrist, social worker and last but not least, the patient and the parents. The importance of such approach has been clearly emphasized by recent data available in the literature. If this comprehensive approach, with sufficient theoretical and practical knowhow, may express the more optimistic hope than Witts (1936) did more than 40 years ago.

REFERENCES

1. AAS, K. : Diagnosis of immediate type respiratory allergy. Pediat. Clin. N. Amer. 22 : 33 (1975).
2. ABRISHAMI, M.A. and THOMAS, J. : Aspirin intolerance — A review. Ann. Allergy L9 : 28 (1977).
3. AMERICAN THORACIC SOCIETY : Chronic bronchitis, asthma and pulmonary emphysema. Amer. Rev. resp. Dis. 85 : 762 (1962).
4. APOLD, J. and AKSNES, L. : Correlation between increased bronchial responsiveness to histamine and diminished plasma cyclic adenosine monophosphate response after epinephrine in asthmatic children. J. Allergy clin. Immunol. 59 : a43 (1977).
5. AVNER, S.E. : Beta-adrenergic bronchodilators. Pediat. Clin. N. Amer. 22 : 141 (1975).
6. BAKER, J., HONG, R,; DICK, E. and REED, C. : Asthma, IgA deficiency, and respiratory tract infections. J. Allergy clin. Imunol. 58 :713 (1976).
7. BARR, L.W. and LOGAN, G.B. : Prognosis of children having asthma. Pediatrics 34 : 856 (1964).
8. BERGHER, L.W. and KASS, I. : A review of some new trends in asthma. Curr. med. Dialogue 16 : 1117 (1972).
9. BIANCO, S.; GRIFFIN, J.P.; KAMBUROFF, P.L. and PRIME, F.J. : Prevention of exerciseinduced ashma by indoramine. Brit. med. J. 4 : 18 (1974).
10. BIERMAN, C.W. : Theophylline in asthma. Pediatrics 58 : 623 (1976).
11. BIERMAN, C.W. : New drugs for asthma : A scientific basis for therapy (Editorial). Chest 72 : 689 (1977).
12. BIERMAN, C.W. : The use of adrenergic bronchodilators in children. Chest 73 (Suppl) : 105 (1978).
13. BIERMAN, C.W.; KAWABORI, I. and PIERSON, W.E. : Incidence of exercise-induced asthma in children. Pediatrics 56 (Suppl) : 847 (1975).
14. BLAIR, H. : Natural history of childhood asthma. 20-year follow up. Arch. Dis. Childh, 52 : 613 (1977).
15. BRANDON, M.L. : Long-term metaproterenol therapy in asthmatic children. J. ame. med. Ass. 235 :736 (1976).
16. BRASHER, G.W. : Etiologic factors in infantile asthma. Ann. Allergy 37 : 246 (1976).
17. BRASHER, G.W. and BOURLAND, P. D. : The role of IgA in the pathogenesis of atopy. Ann. Allergy 34 : 137(1975).
18. BRASHER, G.W.; STARR, J.C.; McCOOMBS III, W.B. and BOURLAND, P. D. : T-lymphocytes in children with allergic respiratory disease. Ann. Allergy 39 : 237 (1977).
19. BRITISH MEDICAL RESEARCH COUNCIL, SUBCOMMITTEE ON CLINICAL TRIALS IN ASTHMA : Cortisone acetate in status asthmaticus. Lancet 2 : 803 (1976).
20. BUFFUM, W.P. and SETTIPANE, G.A. : Prognosis of asthma in childhood. Amer. J. Dis. Child. 112 : 214 (1966).
21. BULOW, K.B. and KALEN, N. : Local and systemic effects of beclomethasone inhalation in steroid-dependent asthmatic patients. Curr. ther. Res. 16 : 1110 (1974).
22. BURANAKUL, B.; WASHINGTON, J.; HILMAN, B.; MANCUSO, J. and SLY, R.M. : Causes of death during acute asthma in children. Amer. J. Dis Child. 128 : 343 (1974).
23. CHAN-YEUNG, M. : The effect of Sch 1000 and disodium cromoglycate on exercise-induced asthma. Chest 71 : 320 (1977).

24. CHOO-KANG, Y.F.J.; SIMPSON, W.T. and GRANT, I.W.B. Controlled com parison of the bronchodilator effects of three beta-adrenergic stimulant drugs administered by inhalation to patients with asthma. Brit. med. J. 2 : 287 (1969).

25. CHURCH, J.A. and RICHARDS, W. : Routine laboratory determinations in pediatric allergic disease. ann. Allergiy 41 : 136 (1978).

26. CLAMAN, H.N. : How corticosteroids work. J. Allergy clin. Immunol. 55 : 145 (1975).

27. CLARK, T.J.H.: Acute severe asthma, In CLARK, T.J.H. and GODFREY, S. : Asthma, p. 303 (Chapman and Hall, London 1977).

28. COLLINS-WILLIAMS, C. : The status of immunotherapy in children — What are the problems? Ann. Allergy 39 : 87 (1977).

29. COLLINS-WILLIAMS, C.; HUNG, F. and BREMNER, K. : House dust mite and house dust allergy. Ann. Allergy 37 : 12 (1976).

30. COTTON, E.K. and PARRY, W.P. : Treatment of status asthmaticus and respiratory failure. Pediat. Clin. N. Amer. 22 : 163 (1975).

31. CROPP, G.J.A. : Exercise-induced asthma. Pediat. Clin. N. Amer. 22 : 63 (1975).

32. CZARNY, D. : Skin tests. Austr. Fam. Physician. 5 Spec. Issue) : 71 (1976).

33. DALAYEUN, H. : Cromoglycate disodique et asthma Ann. Pediat. 20 : 99 (1973).

34. DAVIES, G.; THOMAS, P.; BRODER, I.; MINZ, S.; SILVERMAN, F.; LEZNOFF, A. and TROTMAN, C. : Steroid-dependent asthma treated with inhaled beclomethasone diproprionate. Ann. intern. Med 86 : 549 (1977).

35. DICKSON, W. : Bronchial hyperreactivity in childhood asthma. Update, October 1973. p. 1093.

36. DICKSON, W., HALL, C.E. ELLIS, M. and HORROCKS, R.H. : Beclomethasone diproprionate aerosol in childhood asthma. Arch. Dis Childh. 48 : 671 (1973).

37. DOWNES, J.J.; FULGENCIO, T. and RAPHAELY, R.C. : Acute respiratory failure in infants and children. Pediat. Clin. N. Amer. 19 : 423 (1972).

38. DRUG COMMITTEE OF THE RESEARCH COUNCIL OF ALLERGY : Side effects of prolonged corticosteroid treatment in patients with asthma. J. Allergy 40 : 88 (1967).

39. DUJOVNE, C.A. and AZARNOFF, D.L. : Clinical complications of corticosteroid therapy. A. selected review. In AZARNOFFF'S : Steroid Therapy, p. 27 (W.B. Saunders Philadelphia 1975).

40. EGGLESTON, P.A. : Exercise-induced asthma in children with intrinsic and extrinsic asthma. Pediatrics 56 (Suppl) : 856 (1975).

41. ELLIS, E.F.; KOSOYKO, R. and SOBOL, B.J. : Phar-macokinetics of theophylline in children with asthma. Pediatrics 58 : 542 (1976).

42. EMIRGIL, C.; WESSON, C. and SOBOL, B.J. : Double blind comparison of metaproterenol 10 mg with ephedrine in bronchial asthma. Curr. ther Res. 22 : 368 (1977).

43. EVANS, R.; PENCE, H.; KAPLAN, H. and ROCKLIN, R.E. : The effect of immunotherapy on humoral and cellular responses in ragweed hay-fever. J. clin Invest. 57 : 1378 (1976).

44. FALLIERS, C.J. : Cromolyn sodium (Disodium cromoglycate) prophylaxis. Pediat. Clin. N. Amer. 22 : 141 (1975).

45. FALLIERS, C.J. : Familial coincidence of asthma, aspirin intolerance and nasal polyposis. Ann. Allergy 32 : 65 (1974).

46. FALLIERS, C.J.; CHAI, H.; MOLK L.; BANE, H. and de A. CARDOSO, R.R.: Pulmonary and adrenal effects of alternate day corticosteroid therapy. J. Allergy clin. Immunol. 49 : 156 (1972).

47. FIXLEY, M; SHEN, D.D. and AZARNOFF, D.L. : Theophylline bioavailability. A comparison of the oral absorption of theophylline elixir and two combination theophylline tablets to intravenous theophylline. Amer. Rev. resp. Dis 115 : 995 (1977).

48. FLOD, N.E.; FRANZ, M.L.; GALANT, S.P. : Recent advances in bronchial asthma. Amer. J. Dis. Child. 130 : 890 (1976).

49. FORD, R.M. : The prevention of asthma. Some basic needs. Med. J. Austr. 1 : 294 (1976).

50. FREARS, J.EF.; WILSON, L.C. and FRIEDMAN, M. : Betamethasone 17-valerate by aerosol in childhood asthma. Arch. Dis. Childh. 48 : 856 (1973).

51. GADDIE, J.; SKINNER, C. and PALMER, K.N.V. : Hyposensitization with house dust mite vaccine in bronchial asthma. Brit. J. 2 : 651 (1976).

52. GALANT, S.P. : The effect of metaproterenol in chronic asthmatic children receiving therapeutic doses of theophylline. Chest 73 (Suppl) : 1010 (1978).

53. GALANT, S.P.; GILLMAN, S.A.; CUMMINS, L.H.; KOZAK, P.P. and ORCUTT, J.J. : Reliability of salivary theophylline as a guide to plasma theophylline levels. Amer. J. Dis. Child. 131 : 970 (1977).

54. GARRA, B.; SHAPIRO, G.G.; DORSET, C.S.; SIMONS, F.E.; PIERSON, W.E. and BIERMAN, C.W. : A double blind evaluation of the use of nebulized metaproterenol in hospitalized asthmatic children and adolescents. J. Allergy clin. Immunol. 60 : 63 (1977).

55. GELLER-BERNSTEIN, C.; ZUR, S.; KAHANE, P.; WEISGLASSS, L.; and LAHAV, M. : Serum immunoglobulins in children with asthma associated with severe respiratory tract infections. Ann. Allergy 37 : 127 (1976).

56. GUMEI, A.M.; MILLER, W.F.; MILLER, J. and GAST, L.R. Bronchodilator effect of a new oral beta adrenoceptor stimulant, Th 1165a. A comparison with metaproterenol sulfate. Chest 70 : 460 (1976).

57. GHAZANSHAHI, S.; TOWNLEY, R.; CHAPERONE, E. and VILLACORTE G. : T and B lymphocyte rossettes in bronchial asthma. Ann. Allergy 36 : 324 (1976).

58. GODFREY, S. : Exercise-induced asthma-Clinical, physiological and therapeutic Implications. J. Allergy clin. Immunol. 56 : 1 (1975).

59. GODFREY, S. : The place of a new aerosol steroid, beclomethasone diproprionate, in the management of childhood asthma. Pediat. Clin. N. Amer. 22 : 147 (1975).

60. GODFREY, S. : Childhood asthma, In CLARK and GODFREY'S : Asthma, p. 303 (Chapman and Hall, London 1977).

61. GODFREY, S. and KONIG, P. : Beclomethasone aerosol in childhood asthma. Arch. Dis. Childh. 48 : 665 (1973).

62. GODFREY, S. and KONIG, P. : Treatment of childhood asthma for 13 months and longer with beclomethasone diproprionate aerosol. Arch. Dis Child. 49 : 591 (1974).

63. GODFREY, S.; SILVERMAN, M. and ANDERSON,, S.D. : Problems of interpreting exercise-induced asthma. J. Allergy clin. Immunol. 52 : 199 (1973).

64. GHORY, J.E. : The ABC's of educating the patient with chronic bronchial asthma. Clin. Pediat. (Phila) 16 : 879 (1977).

65.. GOLDGRABER, M.B. : Terbutaline : An effective bronchodilator by inhalation. Ann. Allergy 38 : 127 (1977).

66. GRISLAIN, J-R., MAINARD, R.; CADUDAL, J-L et RIVAL, J.M. : Prevention et traitement de l'etat de mal asthmatique de l'enfant. Ann. Pediat. 20 : 19 (1973).

67. GROVE, D.I.; BURSTON, T.O.; WELLEY, M.L. and FORBES, I.J. : Humoral and cellular immunity in asthma. J. Allergy clin. Immunol. 55 : 152 (1975).

68. HARTLEY, J.P.R.; CHARLES, T.J. and SEATON, A. : Betamethasone valerate inhalation and exercise-induced asthma in adults. Brit. J. Dis. Chest. 71 : 253 (1977).

69. HARTOG, N.; GAAFAR, M.A. and FRASER, R. : Effect of corticosteroids on growth hormone. Lancet 2 : 376 (1964).

70. HENDELES, L.; BURKEY, S.; BIGHLEY, L. and RICARDSON, R. : Unpredictability of Theophylline saliva measurements in chronic obstructive pulmonary disease. J. Allergy clin. Immunol. 60 : 335 (1977).

71. HENDELES, L.; WEINBERGER, M. and WYATT, R. : Guide to oral theophylline therapy for the treatment of chronic asthma. Amer. J. Dis. Child. 132 : 876 (1978).

72. HERMANCE, W.E. and BROWN, E.B. : Long-term use of disodium cromoglycate in bronchial asthma. Ann. Allergy 36 : 423 (1976).

73. HILL, D. : Recent advances in some allergic conditions of childhood. Austr. Fam. Physician 5 (Spec. Issue) : 81 (1976).

74. HILLER, E.J. and MILNER, A.D. : Betamethasone 17-valerate aerosol and disodium cromoglycate in severe childhood asthma. Brit. J. Dis. Chests 69 : 103 (1975).

75. HODSON, M.E.; BATTEN, J.C.; CLARKKE, S.W. and GREGG, I. : Beclomethasone diproprionate aerosol in asthma. Amer. Rev. resp. Dis 110 : 403 (1974).

76. HORTON, D.J. and SPECTOR, S.L. : Clinical pulmonary tuberculosis in an asthmatic patient using a steroid aerosol. Chest 71 : 540 (1977).

77. HUBSCHER, T.T. : Immune and biochemical mechanisms in the allergic disease of the upper respiratory tract : Role of antibodies, target cells, mediators and eosinophils. Ann. Allergy 38 : 83 (1977).

78. HYDE, J.S. and FLORO, L.D. : Theophylline and chlorpheniramine in childhood asthma. Dose requirements for children 6 to 12 years (Therapeutic orphans) and young adults 13 to 18 years of age receiving cromolyn sodium prophylaxis. Ann. Allergy 32 : 73 (1974).

79. HYDE, J.S.; YAMSHON.; ISENBERG, P.D. and SCHUR, S. : Metaproterenol in children with chronic asthma. Clin. Pharmacol. Ther. 20 : 207 (1976).

80. IRANI, F.A.; JONES, N.L.; GENT, M. and NEWHOUSE, M.T. : Evaluation of disodium cromoglycate in intrinsic and extrinsic asthma. Amer. Rev. Dis 106 : 179 (1972).

81. IRONS, J.S.; PRUZANSKY, J.J. and PATTERSON, R. : Immunotherapy : Mechanism of action suggested by measurements of immunologic and cellular parameters. J. Allergy clin Immunol. 56 : 64 (1975).

82. ISHIZAKA, K. and ISHIZAKA, T. : Identification of gamma-E antibodies as a carrier of reaginic activity. J. Immunol. 56 : 64 (1975).

83. ISHIZAKA, K. and ISHIZAKA, T. : Biological function of gamma-E antibodies and mechanism of reaginic hypersensitivity (Abstr). Clin exp. Immunol. 6 : 25 (1970).

84. JENNE, J.W. and CHICK, T.W. : 'Unresponsiveness' to isoproterenol (Editorial). Chest 70 : 691 (1976).

85. JENNE, J.W.; CHICK,T.W.; STRICKLAND, R.D. and WALL, F.J. : A coparison of beta adrenergic function in asthma and chronic bronchitis J. Allergy clin. Immunol. 60 : 346 (1977).

86. JOHNSTONE, D.E. : A study of the natural history of bronchial asthma in children. Amer. J. Dis. Child. 115 : 213 (1968).

87. JOHNSTONE, D.E. : The case for hyposensitization. Its rationale anl justification, Pediat. Clin. N. Amer. 22 : 239 (1975).

88. JOHNSTONE, D.E.; ROGHMAN, K.J. and PLESS, I.B. : Factors associated with the development of asthma and hay fever in children : The possible risks of hospitalization, surgery and anesthesia. Pediatrics 56 : 398 (1975).

89. JONES, R.S.; WHARTON, M.J. and BUSTON, M.H. : The place of physical exercise and bronchodilator drugs in the assessment of the asthmatic child. Arch. Dis. Childh. 38 : 539 (1963).

90. JUNOD, A.F. : Metabolism, production, and release of hormones and mediators in the lung. Amer. Rev. resp. Dis. 112 : 93 (1975).

91. KJELLMAN, N.I.M. and JOHANSSON, S.G.O. : IgE and atopic allergy in newborns and infants with a family history of atopic disease. Acta paediat. scand. 65 : 601 (1976).

92. KLAUSTERMEYER, W.B. and HALE, F.C. : The physiologic effect of intravenous glucocorticoid in bronchial asthma. Ann. Allergy 37 : 80 (1976).

93. KLAUSTERMEYER, W.B. and HALE, F.C. : Respiratory mechanics during daily and alternate-day corticosteroid therapy in asthma. Ann. Allergy 37 : 87 (1976).

94. KONIG, P. : Treatment of severe attacks of asthma in children with nebulized beta$_2$-adrenergic agents. Ann. Allergy 40 : 185 (1978).

95. KOUNIS, N.G. : A R,view : Drug induced bronchospasm. Ann. Allergy 40 : 185 (1978).

96. KRIZ, R.J.; CHMELIK, F.; doPICO, G. and REED, C.E. : A short-term double-blind trial of aerosol triamcinolone acetonide in steroid-dependent patients with severe asthma. Chest 69 : 455 (1976).

97. LANDAY, R.A.; GONZALES, M.A. and TAYLOR, J.C. : Effects of phenobarbital on theophylline disposition. J. Allergy clin. Immunol. 62 : 27 (1978).

98. LARSSON, S.; SVEDMYR, N. and THIRINGER, G. : Lack of bronchial beta adrenoceptor resistance in asthmatic during long-term treatment with terbutaline. J. Allergy clin. Immunol. 59 : 93 (1977).

99. LECKS, H.I. : Explosive asthma in the infant and young child under two years. Clin. Pediat. (Phila) 15 : 135 (1976).

100. LECKS, H.I. : Appraisals of cromolyn sodium and corticosteroids in the treatment of the asthmatic child. Clin. Pediat. (Phila) 16 : 861 (1977).

101. LEIFFER, K.N. and WITTIG, H.J. : Unreliability of maximum mid-expiratory flow rate as sole index of bronchodilator response in chronic asthma. Ann Allergy 38 : 96 (1977).

102. LEUNG, P.; KALISKER, A. and BELL, T.D. : Variation in theophylline clearance rate with time in chronic childhood asthma. J. Allergy clin. Immunol. 59 : 440 (1977).

103. LEVISON, H.; COLLINS-WILLIAMS, C.; BRYAN, T.A.; C.; REILY, B.J. and ORANGE, R.B. : Asthma, Current concept. Pediat. Clin. N. Amer. 21 : 951 (1974).

104. LIEBERMAN, P.; PATTERSON, R. and KUNSKER, R. : Complications

of long-term steroid therapy for asthma. J. Allergy clin. Immunol. 49 : 329 (1972).

105. LIGHT, R.W.; CONRAD, S.A. and GEORGE, R.B. : Clinical significance of pulmonary function tests. Chest 72 : 512 (1977).

106. LIN, M.S.; RABIN, B.S.; LANEVER R. and FIREMAN, P. : Hyper-M-immunoglobulinemia in children with bronchial ashma. J. Pediat. 91 : 222 (1977).

107. LOVERA, J.; COOPER, D.M.; COLINS, WILLIAMS C.; LEVISON, H.; BAILEY, J.D. and ORANGE, R.P. : Clinical and physiological assessment of asthmatic children treated with beclomethasone diproprionate. J. Allergy clin. Immunol. 59 : 371 (1977).

108. MANI, V.; GREEN, F.H.J.; LLOYD, G.; FOX, H. and TURNBERG, L.A. : Treatment of ulcerative colitis with disodium cromoglycate. Lancet 1 : 439 (1976).

109. MARKS, M.B. : Cromolyn sodium prophylaxis in asthmatic children under five. Ann. Allergy 39 : 306 (1977).

110. MASCIA, A.V.; FRIEDMAN, E.A. and KORNFIELD, M.A. : Clinical experience with long-term cromolyn sodium administration in 53 asthmatic children. Ann Allergy 37 : 1 (1976).

111. MATONDANG-SIAHAAN C. : Correlation between house dust and Dermatophagoides pteronyssinus by skin testing. Paediat. Indones. 17 : 229 (1977).

112. MATONDANG-SIAHAAN, C. and BRATAWIJAYA, K. : Disodium cromoglycate in five children with intractable asthma. Paediat. Indones. 17 : 213 (1977).

113. MATTSON, A. : Psychologic aspects of childhood asthma. Pediat. Clin. N. Amer. 22 : 77 (1975).

114. MAY, C.D. : Treatment of allergic disorders with injections of allergen extracts. Pediat. Clin. N. Amer. 22 : 221 (1975).

115. McALLEN, M.K.; KOCHANOWSKI, S.J. and SHAW, K.M. : Steroid aerosols in asthma : An assessment of betamethasone valerate and a 12-month study of patients on maintenance treatment. Brit. med. J. 1 : 171 (1974).

116. McFADDEN, E.R. Jr.; KISER, R.; de GROOT, W. : Acute bronchial asthma : Relations between clinical and physiologic manifestations. New Engl. J. Med. 288 : 221 (1973).

117. McFADDEN, E.R. Jr.; KISER R.; HOMES, B. and deGROOT, W.J. : Small airway disease. an assessment of the tests of pheripheral airway function. Amer. J. Med 57 : 117 (1974).

118. McFADDEN, E.R. Jr.; KISER, R.; de GROOT, W.J.; HOLMES, B.; KIKER, R. and VISER, G. : Controlled study of the effects of single doses of hydrocortisone on the resolution of acute attacks of asthma. Amer. J. Med. 60 : 52 (1976).

119. McNICOL, K.N. and WILLIAMS H.B. : Spectrum of asthma in children. I. Clinical and physiological component. Brit. med. J. 4 : 7 (1973).

120. MEIJER, A. : High risk factors for childhood asthma. Ann. Allergy 37 : 119 (1976).

121. MITCHELL, I.; INGLIS, H. and SIMPSON, H. : Viral infection in heavy bronchitis and asthma in children. Arch. Dis Childh. 51 : 707 (1976).

122. MITCHELL, I.; PATERSON, I.C.; CAMERON, S.J. and GRANT, I.W.B. : Treatment of childhood asthma with sodium cromoglycate and beclomethasone diproprionate aerosol singly and in combination. Brit. med. J. 2 : 457 (1976).

123. MITENKO, P.A. and OGILVIE, R.I. : Bioavailability and efficacy of sustained release theophylline tablet. Clin. Pharmacol. Ther. 16 : 720 (1974).

124. MORITA, Y.; MIYAMOTO, T.; HORIUCHI, Y.; OSHIMA, S.; KATSUHATA, A. and KAWAL, S. : Further studies in allergic identity between house dust and the house dust mite, Dermatophagoides farinae Hughes, 1961. Ann. Allergy 35 : 361 (1975).

NELSON, H.S. : The beta adrenergic theory of bronchial asthma. Pediat. Clin. N. Amer. 22 : 53 (1975).

126. NEUMAN, I. and CRETER, D. : Hereditary complement defect and kinin involvement in asthma. Ann. Allergy 38 : 79 (1977).

127. NIZAMI, R.M. and COLLINS- WILLIAMS, C. : Hyposensitization therapy in allergic disease. Ann. Allergy 35 : 295 (1975).

128. NORMAN, P.S. : Bronchial reactivity and immunotherapy. J. Allergy clin. Immunol. 61 : 281 (1978).

129. NORMAN, P.S. : A review of immunotherapy. Allergy 33 : 62 (1978).

130. OGLE, K.A. and BULLOCK, J.D. : Children with allergic rhinitis and/or bronchial asthma treated with elimination diet. Ann. Allergy 39 : 8 (1977).

131. OREHEK, J.; GAYARD, P.; GRIMAUD, G. and CHARPIN, J : Bronchial response to inhaled prostaglandin F_2-alpha in patients with common or aspirin-sensitive asthma. J. Allergy clin. Immunol. 59 : 414 (1977).

132. PANG, L M.; RODRIGUEZ-MARTINEZ, F.; DAVIS, W.J. and MELLIS, R.B. : Terbutaline in the treatment of status asthmaticus. Chest 72 : 469 (1977).

133. PARRY, W.H.; MARTORANO, F. and COTTON, E.K. : Management of life threatening asthma with intravenous isoproterenol infusions. Amer. J. Dis. Child. 13 : 39 (1976).

134. PAYNE, C.B.,Jr.; CHESTER, E.H. and HSI, B.P. : Airway responsiveness in chronic obstructive pulmonary disease. Amer. J. Med. 42 : 554 (1967).

135. PENNOCK, B.E.; ROGERS, R.M.; RYAN, B.R. and AYERS, L.N. : Aerosol administration of fenoterol hydrobromide (Th 1165a) in subjects with reversible obstructive airway disease. Chest 72 : 731 (1977).

136. PEPYS, J. : Immunopathology of allergic lung disease. Clin. Allergy 3 : 1 (1973).

137. PIAFSKY, K.M.; SITAR, D.S. and OGIELVIE, R.I. : Effect of phenobarbital on the disposition of intravenous theophylline. Clin. Pharmacol. Ther. 22 : 336 (1977).

138. PIERSON, W.E.; BIERMAN, C. and KELLEY V.C.: A double blind trial of of corticosteroid therapy in staus asthmaticus. Pediatrics 54 : 282 (1974).

139. PLUMMER, A.L. : The development of drug tolerance to B_2-adrenergic agents. Chest 62 (suppl.) : 949 (1978).

140. PRINCE, H.E. : Aspirin and cross reactivity (Editorial). Ann. Allergy 39 : 47 (1977).

141. RACHELEFSKY, G.S.; COOLSON, A; SIEGEL, S.C. and STEIHM, E.R. : Aspirin intolerance in chronic childhood asthma. Detected by oral challenge. Pediatrics 56 : 443 (1975).

142. RACKEMAN, F.M. and EDWARDS, M.L. : Asthma in children. New Engl. J. Med 246 : 815 (1952).

143. RANGSITHIENCHAI, P. and NEWCOMB, R.W. : Aminophylline therapy in children : Guidelines for dosage. J. Pediat. 91 : 325 (1977).

144. REBUCK, A.S. : Antiasthmatic drugs. I. Pathophysiological and clinical pharmacological aspects. Med. Progr. 2 (2) : 71 (1975).

145. REED, C.E. : Physiology and pharmacology of beta$_2$-adrenergic agents. Chest 72 (Suppl) : 914 (1978).

146. REED, C.E.; SIMS, J.H. and doPICO, G.A. Bronchodilator effect of ephedrine and theophylline after two to four weeks of repeated dosing. Chest 73 (Suppl) : 1019 (1978).

147. RICHARDS, W. and SIEGEL, S.C. : Status asthmaticus. Pediat. Clin. N. Amer. 16 : 9 (1969).

148. RIMSZA, M.E. : Complications of corticosteroid therapy. Amer. J. Dis. Child. 132 : 806 (1978).

149. ROTH, M.J.; WILSON, A.F. and NOVEY, H.S. : A cooperative study of the aerosolized bronchodilator, isoproterenol, metaproterenol and terbutaline in asthma. Ann. Allergy 38 : 16 (1977).

150. RUBIN, A.E.; MANSUR, A.; SCHEY, G.; SHAHOR, Y. and BRUDERMAN, I. : Reversibility of small airways obstruction after therapy with salbutamol. Chest 71 : 470 (1977).

151. SACKNER, M.A.; SILVA, G.; ZUCKER, C. and MARKS, M.B. : Long-term effects of metaproterenol in asthmatic children. Amer. Rev. resp. Dis 115 : 945 (1977).

152. SAMTER, M. and BEERS, R.F. : Intolerance to aspirin : clinical studies and consideration of its pathogenesis. Ann. intern. Med. 68 : 975 (1968).

153. SCHWARTZ, R.H.; ESS, J.D.V.; JOHNSTONE, D.E.; DREYFUSS, E.M..; ABRISHAMI, A. and CHAI, H. : Al phal-l antitrypsin in childhood asthma. J. Allergy (1977).

154. SETTIPANE, G.A.; PUDUPAKKAM, R.K. and McGOWAN, J.H. : Corticosteroid effect on immunoglobulins. J. Allergy clin. Immunol. 62 : 162 (1978).

155. SHAPIRO, G.G.; TATTONI D.S.; PIERSON, W.E.; KELLEY, V.C. and BIERMAN, C.W. : Physiology of steroid dependent and non-steroid dependent asthmatic youths. Ann. Allergy 38 : 237 (1977).

156. SILVERMAN, M. and ANDREA, T. : Time course of effect of disodium cromoglycae on exercise-induced asthma. Arch. Dis. Childh. 47 : 419 (1972).

157. SILVERMAN, M.; CONOLLY, N.M · BALVOUR-LYNN, L. and GODF S. : Long-term trial of disodium moglycate and isoprenaline in chil with asthma. Brit. med. J. 3 : (1972)

158. SIMI, W.W. and MILLER, W.C. : Clinical investigation of fenoterol, a new bronchodilator, in asthma. J. Allergy clin. Immunol. 59 : 178 (1977).

159. SIMONS, F.E.R.; PIERSON, W.E. and BIERMAN, C.W. : Respiratory failure in childhood status asthmaticus. Amer. J. Dis Child. 131 : 1097 (1977).

160. SIMS, J.; doPICO, G.A. and REED, C.E : Bronchodilating effect of oral theophylline-ephedrine combination. J. Allergy clin Immunol. 62 : 15 (1978).

161. SMITH, J.M. : Prevalence and natural history of asthma in school children. Brit. med J. 1 : 711 (1961).

162. SMITH, P.R.; HEURICH, A.E.; LEIFFLER, C.T.; HENIS, M.M.J. and LYONS, H.A. : A comparative study of subcutaneously administered terbutaline and epinephrine in the treatment of acute bronchial asthma. Chest 71 : 129 (1977).

163. SNYDER, R.D. and SIEGAL, G.L. : An asthma triad. Ann. Allergy 25 : 377 (1967).

164. SOBOL, B.J. and EMIRGIL, C. : Pulmonary fuction tests and the diagnosis of bronchial asthma. Ann. Allergy 37 : 340 (1976).

165. SOUHRADA, J.F. and BUCKLEY, J. M. : Pulmonary fuction testing in asthmatic children. Pediat. Clin. N. Amer. 23 : 249 (1976).

166. SPEIZER, F.E. and DOLL, R. : Observations on recent increase in morta-

lity from asthma. Brit. med J. 1 : 1335 (1968).

167. SPITZER, S.A.; KAUFMAN, H.; KOPLOVITZ, A.; TOPILSKY, M. and BLUM, I. : Beclomethasone diproprionate and chronic asthma. Chest 70 : 38 (1976).

168. STEVENSON, R.D. : Mechanism of anti-inflammatory action of glucocorticoids. Lancet 1 : 225 (1977).

169. SVEDMYR, N.L.V.; LARSSON, S.A. and THIRINGER, G.K. : Development of 'resistance' in beta adrenergic receptors in asthmatic patients. Chest 69 : 479 (1976).

170. SWARTS, C.L. and HYDE, J.S. : Long-term efficacy and safety of nebulized metaproterenol solution in bronchial asthma. Chest 70 : 617 (1976).

171. SZENTIVANYI, A. : The beta adrenergic theory of the atopic abnormality in bronchial asthma. J. Allergy 42 : 203 (1968).

172. TASHKIN, D.P. : Therapeutic advantages of the newer bronchodilator compounds. Chest 71 : 125 (1977).

173. TASHKIN, D.P.; KATZ, R.M.; KERSCHNAR, H.; ARCHELEFSKI, G.S. and SIEGEL, S.C. : Comparison of aerosolized atropin, isoproterenol, disodium cromoglycate and placebo in the prevention of exercise-induced asthma. Ann. Allergy 39 : 311 (1977).

174. TAYLOR, W.W.; OHMAN, J.L. and LOWELL, F.C. : Immunotherapy in cat-induced asthma. J. Allergy clin. Immunol. 61 :: 283 (1978).

175. TAYLOR,B.; NORMAN, A.P.; ORGEL, H.A.; TURNER, M.W.; STOKES, C.R. and SOOTHILL, J.F. : Transient IgA deficiency and pathogenesis of infantile atopy. Lancet 2 : 111 (1973).

176. THOMPSON, P. and FRIEDMAN, M. : Intramuscular salbutamol in treatment of acute exacerbations of childhood asthma. Arch. Dis Childh. 52 : 551 (1977).

177. TINKELMAN, D.G.; AVNER, S.E. and COOPER, D.M. : Assessing bronchodilator responsiveness. J. Allergy clin. Immunol. 59 : 109 (1977).

178. TINKELMAN, D.G.; BRICE, J.; YOSHIDA, G.N. and SADLER, J.7. : The impact of chronic asthma on the developing child : Observations made in a group setting. Ann. Allergy 37 : 174 (1976).

179. TJOKRONEGORO, A. : Proses immunclogi pada asma. Kumpulan Naskah Kongres Ikatan Dokter Paru Indonesia I. (Jakarta 1977).

180. TOOGOOD, J.H.; BASKERVILLE, J.; ERRINGTON, N.; JENNINGS, B.; CHUNG, L. and LEFCOE, N. : Determinants of the response to beclomethasone aerosol at various dose levels : A multi regression analysis to identify clinically useful predictors. J. Allergy clin. Immunol. 60 : 367 (1977).

181. TRAUTLEIN, J.; ALLEGRA, J.; FIELD, J. and GILIN, M. : Paradoxic bronchospasm after inhalation of isoproterenol. Chest 70 : 711 (1976).

182. TUFT, L. : Allergy management in clinical practice, p. 73 Mosby, St. Louis 1973).

183. TUFT, L. : The 'intrinsic' or 'infectious' label (Editorial). Ann. Allergy 38 : 361 (1977).

184. TURNER, K.J.; SUMARMO and MATONDANG-SIAHAAN, C. : Precipitating factors in respiratory allergic disease in Indonesian Children. Clin Allergy 8 : 361 (1978).

185. VOGT, F.; CHERVINSKY, P.; DWEK, J. and GRIEKO, M. : Beclomethasone diproprionate aerosol in the treatment of chronic bronchial asthma. J. Allergy clin. Immunol. 58 : 316 (1976).

186. WALSON, P.D.; STRUNK, R.C. and TAUSSIG, L.M. : Intrapatient variability in theophylline kinetics. J. Pediat. 91 : 321 (1977).

187. WARNER, J.O. : Bronchial provocation tests. Arch. Dis Childh. 52 : 750 (1977).

188. WARREN, S.L. : A new look at type I Immediate hypersensitivity immune reactions. Ann. Allergy 36 : 337 (1976).

189. WEINBERGER, M.M. : Use of ephedrine in bronchodilator therapy. Pediat. Clin. N. Amer. 22 : 121 (1975).

190. WEINBERGER, M.M. HUDGEL, D,; SPECTOR, S. and CHIDSEY, C. : Inhibition of theophylline clearance by troleandomycin. J. Allergy clin. Immunol. 59 : 228 (1977).

191. WELLING, P.G.; LYON, L.L.; CRAfluence of diet and fluid on bioavailability of theophylline Clin. Pharmacol. Ther 17 : 475 (1976).

192. WILLIAMS, N.H.; Jr.; KANE, C. and SHIM, C.S : Treatment of asthma with triamcinolone acetonide delivered by aerosol. Amer. Rev. resp. Dis 109 : 538 (1974).

193. WILIAMS, H.E. and McNICOL K.N. : The spectrum of asthma in children. Pediat. Clin. N. Amer. 22 : 43 (1975).

194. WITTIG, H.J.; McLAUGHIN, E.T.; LEIFER, K.L. and BELLOID, J.D. : Risk Factors for the development of allergic disease : Analysis of 2,190 patient records. Ann. Allergy 41 : 84 (1978).

195. WITTS, L.J. : Prognosis in asthma. Lancet. 1 : 273 (1936).

196. WOOD, D.W. and LECKS, H.J. : Deaths due to childhood asthma. Are they preventable? Clin. Pediat. (Phila) 15 : 677 (1976).

197. YUNGINGER, J.W. and GLEIGH, G.J. : The impact of discovery of IgE on the practice of allergy. Pediat. Clin. N. Amer. 22 : 3 (1975).