Ain Shams University
Institute of Postgraduate Childhood Studies
Department of Medical Studies

Prevalence of Sinusitis among Asthmatic Children and its Relation to the Severity and Type of Asthma

Thesis
Submitted for the fulfillment of
Ph. D. Degree in Childhood Studies
Institute of Postgraduate Childhood Studies
Department of Medical Studies
Ain Shams University
By

Dr. Ahmed Mohammed Rashad Foda
M.B. B.Ch., M. Sc. Pediatrics

Supervised by

Prof. Dr. Mohammed Abdel Salam El Guindi
Professor of Pediatrics
Institute of Hepatology
Monoufia University

Ass. Prof. Dr. Magdy Karam El Din Daif
Ass. Professor in Department of Medical Studies. Institute of Postgraduate Childhood Studies
Ain Shams University

Consultant Dr. Essaad Youssef Khallaf
Consultant and Head of Pediatrics Department
Al Matariah Teaching Hospital -Cairo.

2000

بسم الله الرحمن الرحيم

وما أوتيتم من العلم الا قليلا

صدق الله العظيم

To the souls of my grand-parents and father,
to my mother, two sisters and brother,
to my wife and two children,
I dedicate this work.

ACKNOWLEDGMENT

I am very grateful to Professor **Dr. Mohammed Abdel Salam El Guindi**, Professor of Pediatrics, Institute of Hepatology, Monoufia University, for his sincere, meticulous and keen supervision of this work.

I am also grateful to Assistant Professor **Dr. Magdy Karam El Din Daif**, Assistant Professor in the Department of Medical Studies, Institute of Postgraduate Childhood Studies, University of Ain Shams, for his continuous encouragement and assistance throughout the preparation of this work.

I wish to express my deepest gratitude to Consultant **Dr. Essaad Youssef Khallaf**, Consultant and Head of Pediatrics Department, Al Matariah Teaching Hospital – Cairo for her sincere and generous help and encouragement.

I am very thankful to Professor **Dr. Mahmoud Kadry El Masry**, Professor of Clinical Pathology and Head of Child Health Department, National Research Centre for his supervision of the practical laboratory part of this study.

I wish also to thank **Dr. Nagwa Antoush**, Researcher of Clinical Pathology, Child Health Department, National Research Centre for performing the practical laboratory part of this work.

I am also thankful to Assistant Professor **Dr. Inas El Attar**, Assistant Professor in the Biostatistics Department, National Cancer Institute, Cairo University for her help in accomplishing the statistical analysis of this study.

ABSTRACT

Prevalence of Sinusitis among Asthmatic Children and its Relation to the Severity and Type of Asthma.

El Guindi M.A.S., Daif M.K.E.D., Khallaf E.Y. and Foda A.M.R.

One hundred Egyptian known-asthmatic children were included in the study from the Pediatrics Department of Al Matariah Teaching Hospital-Cairo (50 boys and 50 girls). They were all subjected to the following: full medical and allergic history taking, complete clinical examination, peak expiratory flow rate (P.E.F.R.) recording, inhalant skin sensitivity test, total serum IgE determination by E.L.I.S.A. method, complete blood count, chest x-ray and x-ray of paranasal sinuses. According to the results, they were divided into three groups: group of mild asthma (33 patients), group of moderate asthma (29 patients) and group of severe asthma (38 patients).

The study has proved a relationship between the presence of sinusitis and the degree of severity of asthma among the studied Egyptian asthmatic children, being more common in the severe form. Among those patients with sinusitis, 54.8% had severe asthma, 25.8% had moderate asthma and only 19.4% had mild asthma ($p= 0.049$). The study has also proved the higher prevalence of extrinsic (allergic) type of asthma, than the intrinsic type, among the patients suffering from sinusitis ($p= 0.01$).

Key words:
Asthma in children, sinusitis, peak expiratory flow rate (P.E.F.R.), skin sensitivity test, total serum IgE determination by E.L.I.S.A.

Contents

LIST OF ABBREVIATIONS

ACE : Angiotensin converting enzyme.
ALT : Alanine aminotransferase.
BAL : Bronchoalveolar lavage
BHR : Bronchial hyperresponsiveness
b.i.d. : twice daily.
C.T. : computed tomography.
C.R.S.: Chineese restaurant syndrome.
D.P.I.: Dry powder inhaler.
E.C.P.: Eosinophil Cationic protein.
E.D.N.: Eosinophil derived neurotoxin.
E.I.A.: Exercise-induced asthma.
E.I.B.: Exercise induced bronchospasm.
eNANC: neural excitatory N.A.N.C.
E.P.O.: Eosinophil peroxidase.
F.E.S.S.: Fibre-optic endoscopic sinus surgery.
F.E.V.1: Forced expiratory volume in 1 minute.
F.V.C.: Forced Vital Capacity.
G.E.R.: Gastro-esophageal reflux.
G.N.C.S.F.: Granulocyte colony-stimulating factor.
H.E.P.A.: High efficiency particulate air (filter).
H.P.A.: Hypothalamic Pituitary axis.
I.C.D.: International Classification of diseases.
I.P.P.B.: Intermittent positive pressure breathing.
Ig.E: Immunoglobulin E.
iNANC: neural inhibitory N.A.N.C.
I.L.: Interleukin.
I.S.A.A.C.: International Study of Asthma and Allergies in childhood.
L.T.D.: Leukotriene type D.
L.T.E.: Leukotriene type E.

M.B.P.: Major basic protein.
M.D.I.: Metered dose inhaler.
mR.N.A.: messenger Ribo-Nucleic Acid.
M.S.G.: Monosodium glutamate.
N.A.N.C.: non-adrenergic non-cholinergic nervous system.
N.H.A.N.E.S.: National Health and Nutrition Examination Survey.
N.I.H.: National Institute of Health.
PaO2: Partial arterial oxygen tension.
PaCO2: Partial arterial carbon dioxide tension.
pCO2: partial carbone dioxide tension.
P.D.: provocative dose.
P.E.F.R.: peak expiratory flow rate.
P.G.D.: prostaglandins.
pO2: partial oxygen tension.
P.M.N.L.s: Polymorphonuclear leucocytes.
p.r.n.: per needed.
q.i.d.: four times daily.
RAST: Radio-allergo-sorbent test.
S.A.S.: Statistical analysis system.
T: temperature.
T cells: thymus derived lymphocytes.
Th cells: T helper cells.
t.i.d.: three times daily.
T.M.B.: Tetramethylbenzidine.
T.N.F.: Tumour necrosis factor.
T. S. IgE: Total Serum Immunoglobulin E.
U.R.I.: upper respiratory tract infection.
V.I.P.: vasoactive intestinal peptide.
V/Q : Ventilation/Perfusion.

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION
AND
AIM OF THE STUDY

Asthma is a leading cause of chronic illness in childhood, responsible for a significant proportion of school days lost because of chronic illness. Asthma is the most frequent admitting diagnosis in children's hospitals. As many as 10 to 15% of boys and 7 to 10% of girls may have asthma at some time during childhood.

Asthma may be regarded as a diffuse obstructive lung disease with: 1) hyperreactivity of the airways to a variety of stimuli and 2) a high degree of reversibility of the obstructive process which may occur either spontaneously or as a result of treatment. In addition to bronchoconstriction inflammation is an important pathophysiologic factor, it involves eosinophils, monocytes and immune mediators (Sly, 1996).

In some patients with so-called extrinsic or allergic asthma, attacks follow exposure to environmental factors such as dust, pollens and danders. Often but not always, such patients have increased concentrations both of total IgE and of specific IgE against the antigen implicated. In other patients with clinically similar asthma, there is no evidence of IgE involvement, skin tests are negative and IgE concentrations low. This form of asthma has been called intrinsic (Sly, 1996).

The idea that asthma can be worsened by stimuli affecting the nose and sinuses is centuries old. Studies revealed that there was an increased incidence of sinus abnormalities in individuals with asthma. Overall it has been established that 40 to 50% of both adults and children with asthma have abnormal sinus radiographs (Reid, 1992).

In another study of chronic sinusitis among pediatric patients with chronic respiratory complaints, 73% of children 2 to 6 years of age and 74% of children 6 to 10 years and 30% of children

older than 10 had chronic sinusitis (Nguyen K. et al., 1993).

Sly (1996) reported that sinusitis is one of the factors that may exacerbate asthma or make the disease difficult to treat, and that treatment of sinusitis with antibiotics, intranasal steroids, and oral or topical (3-5 days) decongestants for 3 weeks may improve bronchoconstriction as well as sinusitis.

Also, Reid (1992) has shown that asthma improves with treatment of sinusitis.

In Egypt, Badr El Din and El Khattib (1999) concluded that limited Functional Endoscopic Sinus Surgery (FESS), performed on a small group of asthmatic Egyptian children suffering from chronic rhinosinusitis, was helpful in alleviating most of the allergic pulmonary symptoms.

Information on the prevalence of sinusitis among asthmatic Egyptian children is scarce, for this reason this study was conducted to clarify this problem.

This work aimed to study a group of asthmatic Egyptian children with different clinical severities and to assess the prevalence of sinusitis among them and the relation of sinusitis to the degree of severity and type of asthma (extrinsic or intrinsic). To achieve these goals a battery of different techniques were applied for the diagnosis of both asthma and sinusitis.

REVIEW OF LITERATURE

BRONCHIAL ASTHMA

Asthma is the most common chronic lung disorder and affects persons of all ages. The onset of asthma can occur at any age, although the peak incidence is before the age of 5 years. In childhood, asthma is about 30% more common in males than in females, and the disease tends to be more severe in male children. Beyond puberty, females are affected more commonly than males. Asthma is more common in underprivileged urban areas, colder climates, and industrialized communities. There is a familial predisposition to asthma, with incidence highest among first-degree relatives, but occurrence rates are unpredictable (Lawlor, Tashkin, 1995).

Definition

In 1959, a definition of asthma described it as a syndrome that is characterized by increased responsiveness of the bronchi and the trachea to various stimuli, manifested by widespread narrowing of the airways that changed either spontaneously or as the result of therapy (CIBA, 1959). Recently, this definition was revised: "Asthma is a lung disease with the following characteristics: 1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment; 2) airway inflammation; and 3) increased responsiveness to a variety of stimuli" (Guidelines 1, 1991).
This definition introduces the concept that inflammation of the airways is an important component of the asthma syndrome and acknowledges that lung function may not always return to

normal. These definitions of asthma are descriptive. No single test or biopsy result unequivocally establishes the diagnosis of asthma. This syndrome may actually include a spectrum of diseases with varying pathologic processes and clinical prognoses that we lump together as asthma. Clinicians must rely heavily on the history and physical examination. In children older than 5 years of age, spirometry, patterns of peak flow measurements and, on occasion, challenge procedures can be used to document reversible obstruction of the airways. For younger children objective tests measure obstruction of the airways, but these tests are only available at some research centers. Because asthma is characterized by symptoms that occur episodically, it may be difficult to document the presence of obstruction with a measurement at a particular time (Smith, 1993).

Recently, a group of European physicians have proposed a more clinical definition of asthma: "an episodic wheeze and/or cough in a clinical setting where asthma is likely and other rare conditions have been excluded" (Warner et al., 1989). This definition remains descriptive but is functional (Smith, 1993).

Epidemiology

Studies seeking to determine the prevalence of asthma in a population have used a variety of methods. Questionnaires have been developed to elicit information to support the diagnosis of asthma. Challenge techniques and spirometry have been used, but because of the underlying variability of asthma, sampling at a single time may underestimate disease frequency. In general, physician diagnosis of asthma also vastly underestimates the prevalence of asthma (Speight et al., 1983; Sears, 1991).

Most studies use some variation of the question "does your child have attacks of wheezing?" (Sears, 1991) or "does exertion, stress, cold air, damp weather, or allergen exposure cause your pulmonary symptoms?" (Hopp et al., 1984). The NHANES II considered asthma present if a physician diagnosed it or if a person related that he had "frequent trouble with wheezing during the past twelve months, excluding colds or the flu." (Gergen et al., 1988).

When comparing studies of asthma prevalence around the world, figures vary. The International Study of Asthma and Allergies in Childhood (ISAAC) was designed to allow comparisons between populations in different countries. ISAAC Phase One, reported here, used standardized simple surveys that were conducted among representative samples of school children from centers in most regions of the world. Two age groups (13–14 and 6–7 years) with approximately 3000 children in each group were studied in each center. The 13–14 year olds were studied in 155 centers (56 countries) and the 6–7 year olds were studied in 91 centers (38 countries). There were marked variations in the prevalence of asthma symptoms with up to 15-fold differences between countries. The prevalence of wheeze in the last 12 months ranged from 2.1-32.2% in the older age group and 4.1-32.1% in the younger age group and was particularly high in English speaking countries and Latin America. A video questionnaire completed in the older age group in 99 centers (42 countries) showed a similar pattern. The major differences between populations found in the ISAAC Phase One are likely to be due to environmental factors. The results provide a framework for studies between populations in contrasting environments that are likely to yield new clues about the etiology of asthma (Multi-center study, 1998).

Prevalence, Morbidity, and Mortality

The prevalence of asthma has increased dramatically over the last 30 years, and the clearest evidence for the increase has come from population-based studies of school- aged children and young adults (Crater, 1998).

The NHANES II survey found a 58% increase in asthma diagnoses in children aged 6 to 11 between the first survey (1971-1974) and the second survey (1976-1980) (Gergen et al., 1988). In South Wales, Burr found a 100% increase in the presence of asthma in a survey using the same questionnaire of 12-year-olds in 1988 compared with 1973. (History of asthma any time increased from 6% to 12%, whereas current asthma increased from 4% to 8%) (Burr et al., 1989). Yunginger et al., reviewed records available from the Rochester Epidemiology Project that provides complete outpatient and inpatient medical records for patients in their community (Yunginger et al., 1992). Using standardized criteria for asthma diagnosis and reclassifying some patients as having asthma who were previously diagnosed as having bronchospasm or bronchitis, they found a 58% increase in the prevalence of asthma from 1968 to 1983. This increase occurred mainly in children less than 14 years of age.

In the early 1970s, investigators in Papua New Guinea found a prevalence of 0.28% for asthma in the adult population and no asthma at all in the children (Dowse et al., 1985). When this group was restudied 10 years later, the prevalence had risen to 7.3% in adults and to 0.6% in children (Gergen et al., 1990). In investigating possible causes for this extraordinary increase in asthma, the investigators found that the dust mite, which had previously been unknown in that area, was now present in very high quantities. They traced the source of this to blankets that

had been given to the villagers. A proportion of villagers had subsequently made IgE antibodies to dust mite and were among the subjects in whom asthma developed (Dowse et al., 1985). Populations found to have a very low prevalence of asthma, less than 1%, usually have a higher frequency of asthma in the adult population, whereas in areas having a higher prevalence of asthma the reverse is true (Smith, 1989).

Evidence exists that the severity of asthma may be increasing. In the United States from 1979 to 1987, hospital admissions for asthma increased at a rate of 4.5% per year in children less than 18 years of age, with the greatest increase in children less than 5 years of age (Weiss, Wagener, 1990). These children also appeared to have more severe disease. From 1979 to 1983, 0.11% of these admissions required cardiopulmonary resuscitation or intubation, whereas from 1984 to 1987, this figure had risen to 0.5% (Gergen et al., 1990). Many other countries report similar observations concerning increasing rates of hospital admission (Chan et al., 1989; Buist, Vollmer, 1990).

Data derived from other epidemiologic studies show increases in U.S. prevalence through 1994. These data on measures of morbidity show complex longitudinal patterns but are notable for large differences in emergency department services and hospitalizations by age and race. Very recent trends for U.S. asthma mortality suggest widening of an existing racial gap. Limited comparisons are possible between these U.S. trends and international trends but do suggest that U.S. increases in prevalence and mortality rates may reflect world-wide patterns. Also, within the U.S., it is clear that geographic variation exists in asthma prevalence, morbidity, and mortality rates. Changes in certain environmental risk factors and exposures may contribute to recent trends, but little information is available relating specific risk factors to either longitudinal asthma trends,

geographic variability, or high-risk populations (Grant et al., 1999).

This same pattern is reflected in the death rate from asthma. Overall in the United States, deaths from asthma increased 31% from 1980 to 1987. The most rapid rise occurred in children less than 5 years of age (Weiss, Wagener, 1990). Interestingly, four geographic areas have the greatest increase in asthma mortality: New York City; Cook County, Chicago; Maricopa County, Arizona; and Fresno, California. Cook County and New York City alone accounted for 21% of the deaths in the 5- to 34-year-old group! Although the percent of asthma deaths is higher in the nonwhite population than in the white population, the rates of increase are similar in both groups (Weiss, Wagener, 1990). This increase in asthma death rates has been reported in other countries, including Canada, United Kingdom, France, Germany and Denmark ((Buist, Vollmer, 1990).

Epidemiological studies conducted in Egypt to determine the prevalence of asthma in primary school children showed differences in the prevalence rates in different governorates.

In 1989, Awadh reported a rate of 3.01% of asthma among school children aged 6-12 years in Tanta city at Gharbia governorate.

El-Hefny conducted a large epidemiological study in children 3-15 years old in Cairo on 1994 and found an asthma prevalence of 8.2% among them.

Atef reported on 1995 a prevalence of asthma in 11.4% of children aged 6-12 years in El-Salam District in Port-Said governorate.

Haggag (1996) showed that asthma occurs in 5.5% of primary school children, 6-11 years old, in Sharkia governorate.

The reasons for the increase in prevalence, morbidity and mortality are not clear. Despite changes in the way asthma is coded (ICD-version 9 in 1979 resulted in asthmatic bronchitis

being coded as asthma instead of bronchitis) and possible increases in physician ability and willingness to diagnose asthma, it appears that a true increase in prevalence has occurred. Possible explanations include increases in outdoor air pollution, increases in indoor air pollution because energy-efficient homes allow poorer air exchange, increases in adverse drug effects, and changes in availability and use of health care (Tepper et al., 1986; Martinez et al., 1988). Increases in day care use with subsequent increases in exposure to viral infections, maternal smoking rates, and a larger cohort of low birth weight infants surviving with subsequent increased risk of obstructive lung diseases are also factors (Chan et al., 1989).

Risk factors for asthma

A variety of factors have been associated with a higher frequency of asthma. When these are present, an increased risk exists that a child will have asthma.

Sex:

In children before the age of 10, asthma is diagnosed more frequently in males, with male/female ratios ranging from 1.4:1 to 2:1 (Mak et al., 1982; Lee et al., 1983; Gergen et al., 1988). Boys and girls experience a similar frequency of positive skin tests to allergens, but boys have a higher incidence of bronchial lability (Verity et al., 1984). Infant boys as a group appear to have smaller airways relative to lung size than do girls (Tepper et al., 1986). In a prospective study, it was shown that infants with lower values for lung function are more likely to wheeze with a respiratory infection (Martinez et al., 1988). It is also generally stated that asthma tends to be more severe in young

boys than girls (Williams, McNichol, 1969; Dodge, Burrows, 1980). Weiss found that for the diagnosis of asthma, the male/female ratio was 1.8:1 (Weiss et al., 1980). When a history of recurrent wheezing was used instead, the ratio was 1:1, suggesting that semantics may play a role. After age 10, the male preponderance tends to lessen. Studies that follow children into adulthood generally find that there is no sex difference in prevalence or prognosis (Peat et al., 1992).

Age:

Among childhood asthmatics, one third will have the onset of their symptoms before the age of 2, and 80% will have symptoms before age 5 (Siegel, Rachelefsky, 1985; Croner, Kjellman, 1992). In the past, it was suggested that asthma starting before 12 months of age was associated with more severe and persistent asthma (Buffum, Settipane, 1966). However, several recent studies emphasized that the frequency of asthma attacks and the need for continual medication during childhood are more important indicators for persistence of asthma than age of onset before 1 year (Martin et al., 1982; Park et al., 1986; Kelly, 1987). One study found that wheezing that began after age 2 was associated with a greater persistence of wheezing at age 11, as compared with wheezing that began before age 2 (81% versus 24%) (Sporik et al., 1991).

In the United States, children 6 to 14 years of age whose asthma was reported to begin after age 2 or 3 reported having more active asthma in the 12 months preceding the survey. However, when the same data were analyzed for ages 5 to 24, no association was found between asthma severity and age of onset (Gergen, Weiss, 1992). This may be an artifact caused by faulty recall. Surveys that rely on histories of events note that when

groups have been followed up prospectively and resurveyed at intervals of 5 to 10 years, a significant decrease is found in reporting previous episodes of asthma symptoms (Peat et al., 1992). At age 16, the estimate of lifetime prevalence of wheezing based on parent recall was 4.5%. However, when this was merged with computer data obtained from the same children at age 7 and age 11, the cumulative incidence was 24.5%! (Anderson et al., 1992).

Race:

In the United States, the prevalence rate for asthma among black children is higher than among white children. Data from one survey found a prevalence of asthma in the first grade of 12% black and 7.2% white (Mak et al., 1982). Another survey found a 9.4% prevalence of asthma in black children and 6.2% prevalence in white children (Gergen, 1988). After adjusting for age and sex, black children still had approximately 2.5 times as much asthma and 1.5 times as much history of frequent wheeze (Schwartz et al., 1990). Even when younger maternal age, residence in the central city, and family income were included in the adjustment, blacks still had a higher risk for asthma developing (Schwartz et al., 1990). This means that in the United States, independent of socioeconomic factors, black children have a higher prevalence of asthma than do white children. An explanation may be the smaller lung volumes for a given height demonstrated in this black population, with a possible predilection to wheeze with smaller lung volumes (Schwartz et al., 1988). A greater readiness to diagnose asthma may also be a factor. Among children with asthma, frequent wheeze was reported in 62% of white children and 58% of black children. However, among children who reported frequent wheeze, asthma

was diagnosed 1.9 times as frequently in black children (Schwartz et al., 1988).

In England, children who have similar socioeconomic and environmental background have very similar prevalence figures for asthma regardless of races (Johnston et al., 1987). New Zealand also reports similar prevalence figures for European or Maori children (Harrison et al., 1986).

Atopy:

Coca and Cooke coined the word atopy long before IgE was discovered. They meant it to apply to a group of diseases, allergic rhinitis, asthma, and atopic dermatitis, that tended to cluster in families and that often had positive immediate skin tests that correlated with symptoms on exposure to a specific allergen. Although it is now known that some asthma and atopic dermatitis can occur in non-allergic persons without any positive skin tests, these illnesses are still considered atopic. In various studies the word atopy may mean elevated IgE; the presence of positive skin tests alone; the presence of positive skin tests with associated symptoms; or the presence of asthma, allergic rhinitis, or atopic dermatitis regardless of IgE levels or skin tests results (Smith, 1993).

In epidemiologic studies evidence has been found that asthma and immediate hypersensitivity are inherited separately, but that allergy seems to aggravate the severity of the asthma (Sibbald et al., 1980; Zimmerman et al., 1988). IgE levels, allergic rhinitis, and positive skin tests were significantly greater in the more severe asthmatic patients of the Australian group studied at age 28 than in the less severe asthmatic patients or controls (Kelly et al., 1987). However, this must be viewed in the context that the incidence of positive skin tests is highest in young subjects;

it peaks between 25 and 34 years of age and declines after age 55 (Barbee et al., 1987).

Overall, 75% to 80% of patients with asthma have positive skin tests to common inhalant allergens (Nelson, 1985). The nature of the allergen also may have an effect on the development of asthma. Sears found that children with positive skin tests to dust mite or cat were more likely to have asthma develop, whereas those with positive skin tests to grasses did not have an increased asthma risk (Sears et al., 1989). A prospective study of children at risk for the development of allergic disease because at least one parent was atopic showed that early childhood exposure to house dust mite allergen was an important determinant in the subsequent development of asthma (Sporik et al., 1990). Those children exposed to more than 10ug. Der p I (major mite allergen) per gram of dust in infancy had a 4.8 times greater risk of active asthma at age 11 than children exposed to lower levels of mite allergen. Children in this group who wheezed before age 5 but were not still wheezing at age 11 had no correlation with atopy or mite sensitivity. This suggests that those found to wheeze with viral respiratory infections only in early childhood may identify a separate population from the allergic asthmatic children whose wheezing persists.

When young children with asthma were studied, a subgroup of highly atopic children could be identified (Zimmerman et al., 1988). These children produced specific IgE to foods in the first year of life and to inhalant allergens between the first and second year of life, well before the inhalant allergens could be demonstrated to be provoking symptoms. They tended to have IgE levels that were 10 times higher than control children, and they tended to have more severe protracted asthma develop. However, the tendency to develop asthma with viral infections in

infancy appeared to be independent of atopy. Many of these infants who wheezed with viruses had no evidence of atopy.

In asthmatic patients, other atopic diseases are more prevalent. Although allergic rhinitis exists in approximately 5% to 9% of children (Broder et al., 1974), 28% to 61% of asthmatic patients may have associated allergic rhinitis (Blair, 1977; Barbee et al., 1987). This peaks at ages 16 to 24, with prevalence rates as high as 67% in more severe asthma (Kelly et al., 1990), As many as 50% of asthmatic children have some atopic dermatitis (Martin et al., 1981; Gerritsen et al., 1990). However, by age 28, presence of eczema was not related to asthma severity (Martin et al., 1981).

Coexistence of childhood atopic dermatitis with asthma does not appear to correlate with persistence of asthma into adulthood. Persistence of atopic dermatitis into adulthood, however, may be more likely associated with persistence of severe asthma (Martin et al., 1988). Finally, to confuse the subject further, Burrows has found that the IgE level, regardless of the presence of positive skin tests, correlates with the prevalence of asthma (Burrows et al., 1989). In a group of 2657 subjects, no asthma was present in 177 subjects with the lowest IgE for age and sex, and the odd ratio for asthma increased linearly with the IgE level. In contrast, the subjects with allergic rhinitis were associated primarily with skin test reactions to aeroallergens independent of serum IgE level. Their conclusion was that asthma is almost always associated with some type of an IgE-related reaction and hence has an allergic basis even if specific IgE could not be identified. Burrows argued strongly against the division of asthma into extrinsic (allergic) versus intrinsic (nonallergic) types. Sears reported that bronchial hyperreactivity in 11-year-old children tended to be associated with the level of IgE regardless of any positive skin test or other

atopic disease, even if they had never had symptoms of asthma (Sears et al., 1991). Clough, in a study of 7 and 8 year olds found that atopic children are more likely to have more persistent and perennial symptoms, whereas nonatopic children were more likely to have clinical episodes of wheezing only in relationship to a viral infection (Clough et al., 1991). Inouye found no difference in severity of asthma in either skin test-positive or skin test-negative adult asthmatics when their condition was adjusted for age and duration of asthma (Inouye et al., 1985). This suggests that in childhood, asthma associated with positive skin tests has a worse prognosis, but that in adulthood, this connection is lost (Smith, 1993).

Pathophysiology

The signs and symptoms of asthma are caused by anatomic narrowing of the tracheobronchial airways and the resultant 1) increased resistance to airflow, 2) overinflation of the lung, 3) uneven distribution of ventilation with regional hypoventilation in relation to pulmonary blood flow (reduced V/Q) causing hypoxemia, and 4) increased ventilation drive (Lawlor, Tashkin, 1995).

Pathology

Microscopic assessment of specimens from subjects dying of asthma has shown airways occluded with mucus, serum proteins, cellular debris, and intact cells. Much of the epithelium lining the airways is sloughed into the lumen. Hypertrophy of submucosal glands and bronchial smooth muscle and dilation of blood vessels are seen. The basement membrane, which was previously thought to be thickened because of its appearance

under light microscopy, is actually normal (Kay, 1991). Beneath the basement membrane, in asthma a dense deposition of collagen fibrils made up of collagen types III and V with fibronectin is seen (Djukanovic et al., 1990). A prominent infiltration with inflammatory cells, especially eosinophils and lymphocytes has been found.

Evidence of inflammation is also seen in milder asthmatic conditions. These patients have infiltration of eosinophils that is less intense than in those dying from asthma. Even in mild asthma there is hypertrophy and hyperplasia of submucosal glands and an increase in the number of goblet cells. The mucus produced has a higher concentration of glycoproteins and is therefore more viscous. Mucociliary clearance is decreased (Laitinen et al., 1989).

Eosinophils:

The most distinctive feature of asthma is the presence of eosinophils (Djukanovic et al., 1990). Mainly located in the skin or mucosa of patients with allergic diseases, eosinophils contribute directly to tissue damage and chronic inflammation (Desreumaux, Capron, 1996). In fact, some have suggested that asthma be considered a chronic eosinophilic bronchitis. Eosinophils contain four cationic granule proteins capable of causing tissue damage (Weller, 1994). Major basic protein (MBP) resides in the crystalloid formations of the cell, whereas eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN) are contained in the matrix of the granules. The eosinophil can cause tissue damage by the elaboration of oxygen-derived metabolites, such as superoxide and hydrogen peroxide, working with EPO, as well as direct cytotoxic activity of MBP and ECP (Venge et al., 1991),

MBP can directly abolish ciliary activity and cause denudation of airway cells (Gleich, 1990). ECP can be identified in large amounts in the bronchial mucosa of asthmatic patients. The number of eosinophils obtained in bronchoalveolar lavage (BAL) fluid correlates with the severity of the asthma (Bousquet et al., 1990), and the number of activated eosinophils correlates with the degree of bronchial hyperresponsiveness (BHR) (Bradley et al., 1991).

Mast Cells:

Mast cells play a prominent role in asthma. One half of the lung mast cells can be found in the bronchioles and bronchi below the basement membrane, whereas the other half are in the intra-alveolar septa (White, Kaliner, 1991). All of the mast cells are adjacent to capillaries. Studies from BAL show the numbers of mast cells are increased by 3-fold to 5-fold in asthmatic subjects. The mast cells identified in the airways of asthmatic subjects are mucosal mast cells containing neutral proteases (as opposed to connective tissue mast cells) (Schwartz, 1994). IgE fixes to high- affinity receptors Fc RI on the mast cells. Allergen or other non-immunologic stimuli can cause release of the mast cell granule contents. Mast cell secretogogues include hypoxia, complement products C5a and C3a, histamine- releasing factors from other cells such as eosinophils, mononuclear cells, lung macrophages, neutrophils, and platelets, as well as IL-1, IL-3, and granulocyte colony-stimulating factor (GMCSF), and neuropeptides such as substance P. After mast cell degranulation, both serum and BAL fluid histamine increases. Oxidative metabolites of arachidonic acid are generated and secreted. By way of the cyclooxygenase system, prostaglandins and thromboxanes are formed, and by way of the lipoxygenase

system leukotrienes are generated. PGD2 is the most abundant mast cell prostaglandin. These mediators cause edema, vascular permeability, and bronchonconstriction. The early phase of the allergic reaction is caused primarily by release of mast cell mediators (Djukanovic et al., 1990).

Macrophages:

Most cells recovered from BAL in both normal subjects and asthmatic subjects are macrophages. A substantial increase is seen in the number of macrophages retrieved after a positive antigen challenge. Macrophages release many important mediators of inflammation. They can generate arachidonic acid metabolites by both the lipoxygenase and cyclooxygenase pathways. They produce platelet activating factor (PAF), which is an important activator of eosinophils (Djukanovic et al., 1990). They also elaborate IL-1, IL-8, tumor necrosis factor (TNF), GMCSF, and histamine- releasing factors (Montefort et al., 1992; Lemanske, 1992). Alveolar macrophages can secrete also IL-10 and IL-12 that regulate Th2 response in asthma. IL-10 deactivates T cells and IL-12 reorients the response toward a Th1 pattern (Magnan et al., 1998).

Neutrophils and Platelets:

The role of neutrophils in asthma is unclear. Their number is not usually increased in biopsy specimens of epithelium or in BAL from asthmatic subjects, except in certain occupational exposures (Djukanovic et al., 1990). They have numerous inflammatory mediators, but evidence that they are directly involved in producing the inflammation of asthma is inadequate. Platelets also contain many inflammatory mediators, but direct

evidence of their participation in asthma pathogenesis is lacking (Djukanovic et al., 1990).

Lymphocytes:

Increasing evidence exists that T cells play an important role in the generation of airway inflammation. In fact, asthma may be a T cell-mediated disease (Rochester, Rankin, 1991). Increased numbers of T cells are found in the airways of those dying of asthma (Litchfield, Lee, 1992). Increased numbers of activated $CD4^+$ cells have been demonstrated in the peripheral blood of those hospitalized with acute severe asthma. As these patients improved, the level of activated $CD4^+$cells decreased. The numbers of activated T cells were highest in the nonatopic asthmatic subjects, but atopic asthmatic subjects had higher levels than nonasthmatic controls (Corrigan, Kay, 1990). Nonallergic asthmatic subjects have also been shown to have more $CD4^+$ T cells and macrophages in the bronchial mucosal biopsy specimens than do allergic asthmatic subjects. This suggests that T cells may play a major role in regulating inflammation, particularly in the nonallergic asthmatic patient (Bentley et al., 1992).

The $CD4^+$ cells retrieved from BAL express mRNA for IL-3, IL-4 and IL-5 and GMCSF but not for interferon gamma. This picture is typical of a specific subset of helper cells described in mice, called Th2 cells. These cells promote B cell production of immunoglobulins and elaborate IL-10, which inhibits Th1 cells.

Th1 cells are helper cells involved in delayed-type hypersensitivity reactions. The Th1 cells make interferon gamma that suppresses Th2 cell function. Th2 cells may play an important role in directing the inflammatory response. IL-4 is a mast cell growth factor and promotes switching of B cell

isotypes to secrete IgE. IL-5 promotes differentiation, adhesion, and survival of eosinophils (Robinson, 1992).

Because T cells (Th2) can produce eosinophil chemotactic factors, regulate IgE production, and generate factors that can activate mast cells, T cells appear to be involved in most aspects of the production of inflammation in asthma. They are capable of initiating and propagating inflammatory reactions in asthmatic patients (Romagnani, 1994).

Bronchial Epithelium:

The bronchial epithelium itself plays an active role in asthma. It produces a relaxing factor that the toxic products of eosinophils destroy (Djukanovic et al., 1990). It also produces IL-16 that is involved in the pathogenesis of asthma through its ability to selectively induce $CD4^+$ recruitment within the inflamed bronchial wall (Laberge et al., 1997). The epithelium also can generate the oxidative products of arachidonic acid that can facilitate disruption of the epithelium. When the epithelium is sloughed into the lumen, hyperreactivity of the airways markedly increases. The loss of the ciliated epithelium plus the cellular debris clogging the airway further impair mucociliary clearance (Smith, 1993).

Low- affinity IgE Receptors (Fc RII):

Macrophages, monocytes, eosinophils, lymphocytes, and platelets have low-affinity receptors for IgE. Circulating IgE can fix to these cells and is capable of stimulating these cells to release their inflammatory mediators when combined with antigen or other stimuli (Kay, 1991).

Neurogenic Mechanisms:

Studies of allergic asthmatic subjects have revealed a decreased sensitivity of the beta- adrenergic receptors to any stimulus. This beta- adrenergic blockade, elegantly described by Szentivanyi in 1968, has been shown to be present in airways, cells, and vasculature in these subjects (Szentivanyi, 1968; Shelhamer et al., 1980). It contributes to decreased sensitivity to endogenous catecholamines, leading to less bronchodilator opposition to vagal constrictor tone. Sensitivity is increased to cholinergic stimulation in allergic and asthmatic subjects, both in the lungs and other organs (Kalliner et al., 1982). Asthmatic subjects also have heightened sensitivity to alpha- adrenergic stimuli, whereas nonasthmatic allergic subjects do not (Henderson et al., 1979). Each of these autonomic aberrations contributes to the pathologic condition of asthma: smooth muscle constriction, mucus secretion, and edema.

The nonadrenergic noncholinergic (NANC) nervous system provides the principal neural inhibitory pathway (iNANC) in human airways and promotes bronchodilation. It also contains the excitatory pathways (eNANC) that are part of the sensory network capable of stimulating reflex bronchoconstriction. Several neuropathies have been identified as mediators of this system. Vasoactive intestinal peptide (VIP) is the most potent endogenous bronchodilator known and may be the principal neurotransmitter of the iNANC inhibitor system. No distinct abnormality of this system has been identified in asthma. However, mast cell tryptase is capable of degrading VIP (Barnes et al., 1991).

Substance P and neurokinin A belong to a group of peptides called tachykinins found in afferent ganglia and unmyelinated sensory nerves (C fibres). These substances, as well as others

such as calcitonin-in-gene related peptide are released from sensory nerves by means of axon reflexes in response to irritant stimuli. They cause increase in vascular permeability and bronchoconstriction and aggravate edema contributing to the inflammatory reaction. When the airway epithelium is damaged, the tachykinins augment the reaction allowing even more constriction, microvascular leakage, and mucus secretion (Barnes, 1992)

Inflammation:

The cytokines, mediators, cells, and neurogenic factors combine to produce an inflammatory reaction in the asthmatic airway. The inflammation causes the walls of the bronchi to be thickened in both the membranous and cartilaginous airways. It has been demonstrated that if the bronchial smooth muscle is constricted by 40% in a normal airway, there is a 15-fold increase in resistance to air flow. The same degree of smooth muscle constriction in an inflamed airway causes a 290-fold increase in resistance (Bleecker, 1985). The inflammation also leads to a state of bronchial hyperresponsiveness (described later).

Physiology

Physiologic Events:

The net effect of constriction of bronchial smooth muscle, edema, and inflammation of airways and mucus secretion is to produce airways that are narrow. The decreased caliber of airways is unevenly distributed throughout the lung. The greater the narrowing of the airways the greater is the resistance to

airflow. This means that more effort is needed to operate the bellows (the lung) that move air (Smith, 1993).

Early in an asthma attack decreased pO_2 ensues because of ventilation-perfusion mismatching. This hypoxia leads to hyperventilation. There is a mild decrease in pO_2 and pCO_2 and a slight increase in pH, a respiratory alkalosis. Measurements of air flow, such as FEV_1, peak expiratory flow rate (PEFR), and FEF_{25-75} (a flow rate that reflects small airways function when FEV_1 is normal) are decreased (McFadden et al., 1973).

As the episode worsens, ventilation-perfusion abnormalities worsen and pO_2 drops further. Smaller airways are not able to empty even during the prolonged expiration and air trapping results. The total lung volume and the residual volume increase. This means that the child is breathing at a higher lung volume, which is a less efficient way to breathe (uses more energy and contributes to fatigue), but helps to keep the airways open, allowing better gas exchange. During this phase, the pCO_2 drops even lower and the pH rises higher. Flow rates continue to drop (Smith, 1993).

If the attack persists, the child continues to breathe at even higher lung volumes against greater resistance. These two factors are responsible for the sensation of dyspnea. Finally, the child cannot work hard enough to move the volume of air necessary to exchange the CO_2. The pCO_2 begins to rise and the pH falls. In a severely distressed asthmatic subject who is working hard to breathe, a pCO_2 of 40 and a pH of 7.40 are not "normal" values but indicators of impending respiratory failure (Smith, 1993).

As the hyperinflation continues, more negative pleural pressure is generated during inspiration. This causes an increased afterload on the right ventricle, allowing a fall in systolic pressure with each inspiration. This is measured by comparing systolic blood pressure during inspiration and expiration. The presence of pulsus

paradoxus (the systolic pressure during inspiration minus the systolic pressure during expiration) greater than 15 to 20 mm. Hg. correlates with an FEV_1 well below 50% of predicted (Rebuck, Read, 1971).

In patients capable of performing a peak flow maneuver or spirometry, these objective measurements of lung function can be helpful in following the response to therapy in the moderately severe asthma attack. In general, if these values are higher than 35% of predicted, CO_2 is not retained (McFadden, Lyons, 1968). Pulse oximetry can give an estimate of oxygenation. However, only the measurement of arterial pCO_2 can be used to follow respiratory failure. Thus, arterial blood gas determinations are still necessary in the severe asthma attack or in distressed children who cannot cooperate with lung function testing (Smith, 1993).

Perception of asthma:

It has been repeatedly shown that asthmatic subjects perceive the severity of their asthma very poorly (Chai et al., 1975). In patients recovering from acute asthma attacks, McFadden showed that significant decreases in FEV_1 and FEF_{25-75} persisted when symptoms of wheeze and dyspnea and use of accessory muscles of respiration had ceased, and the patients considered themselves asymptomatic (McFadden et al., 1973). In another study, both patients and their physicians showed themselves unable to estimate their peak flow during routine visits (Britton et al., 1986). When bronchoconstriction is induced in asthmatic subjects through inhalation challenge, those asthmatic subjects who have lower initial lung function or greater bronchial hyperreactivity (BHR) show much less ability to recognize constriction (Burdon et al., 1982). Some subjects were unable to

recognize any symptoms of asthma when the FEV_1 was reduced by more than 50% (Rubinfeld, Pain, 1977). This renders the routine measurement of some measure of pulmonary function, be it peak flow rate or spirometry, absolutely critical to the assessment and management of asthma. During asymptomatic periods, spirometric measurements are necessary to confirm that the physiology is normal as is suggested by the lack of symptoms. Day-to-day monitoring of PEFR is quite helpful in following asthmatic subjects. This measurement allows one to identify labile asthmatic subjects whose PEFR may be much lower in the morning compared with the evening (Smith, 1993).

Bronchial hyperreactivity:

Hyperresponsiveness of the airways has been cited as one of the key features (Hargreave et al., 1981; Bleecker, 1985; Cockcroft et al., 1987). The clinical characteristics of sudden onset of symptoms following a stimulus (such as cold air or exercise), the tendency to have nocturnal asthma symptoms, and the tendency to experience severe exacerbations have been attributed to the degree of bronchial hyperresponsiveness present. Hyperresponsiveness has been believed to be a reflection of the underlying inflammation of the airways (Holgate et al., 1987). Tests of BHR are used in a variety of protocols. They may be used to assess prevalence of BHR in a population, assess mechanisms of activity and effectiveness of drug therapy, evaluate asthma severity, or to explain facets of physiology. Consequently, it is important for the pediatrician to understand how these tests are performed and interpreted.

In the laboratory, BHR can be assessed in many ways. Cold dry air, hypertonic saline, methacholine, or histamine can be inhaled to provoke a bronchoconstrictor response.

Exercise challenge provides a similar but less sensitive provocation of BHR (O'Byrne et al., 1982; Chatham et al., 1982). All of these challenges can be undertaken in a subject regardless of the presence of allergy. Therefore, they are referred to as tests of nonspecific bronchial hyperreactivity.

The most frequently used tests of nonspecific bronchial hyperreactivity are inhalation challenges with either histamine or methacholine (Chai et al., 1975; Hargreave et al., 1981). A subject undergoes baseline spirometry to measure FEV_1 . Provided the subject can perform the maneuver consistently and his FEV_1 is at least 80% of predicted (some studies will use 70% of predicted or 70% of his "best ever" measurement), the test is begun. First, saline is inhaled and FEV_1 is measured. Provided this measurement does not decrease by greater than 10%, methacholine or histamine is delivered, either by continuous nebulization for 2 minutes with tidal breathing, or by means of a dosimeter that delivers a controlled amount, for five breaths. Either delivery method and both chemicals yield similar results (Juniper et al., 1978; Britton et al., 1986). The dose delivered is very small. FEV_1 does not decrease by 20% or more below the post saline baseline, the next dose is delivered. The procedure continues until a predetermined dose of chemical is delivered or the FEV_1 decreases by 20%. The results are plotted FEV_1 expressed as percent of post saline baseline on the y-axis and dose of the chemical, logarithmically expressed, on the x-axis. A line is dropped from the FEV_1 point that corresponds to 80% of the baseline value down to the axis. This is the concentration of the chemical that caused a 20% drop in FEV_1 and is usually expressed as PD_{20} (for provocative dose causing a 20% fall in FEV_1). This is illustrated in Figure 1 , which depicts bronchial inhalation challenge results graphically.

Most investigators consider a PD_{20} of 8 mg. Histamine or less to be a positive test for BHR. More variability exists with the endpoint for a methacholine inhalation challenge, with either 10 or 25 mg methacholine considered positive. No exact endpoint is diagnostic of asthma. BHR is distributed in a unimodal fashion in the general population (Cockcroft et al., 1983). This is consistent with a heterogeneous disorder resulting from both genetic and environmental factors. Methacholine or histamine sensitivity corresponds fairly closely with the severity of asthma, as demonstrated by measurements of diurnal variation of peak flow and by medication requirements (Ryan et al., 1982; Britton et al., 1988). Good evidence also exists that the degree of hyperresponsiveness is related to the extent of inflammation in the airways (O'Byrne et al., 1987).

Exactly what causes airway hyperreactivity is unknown. Airway epithelial damage, edema in and around the airways walls, stimulation of the noncholinergic excitatory fibres or inhibition of the nonadrenergic inhibitory system, or change in responsivity of the airway smooth muscle have all been postulated (Hargreave et al., 1986).

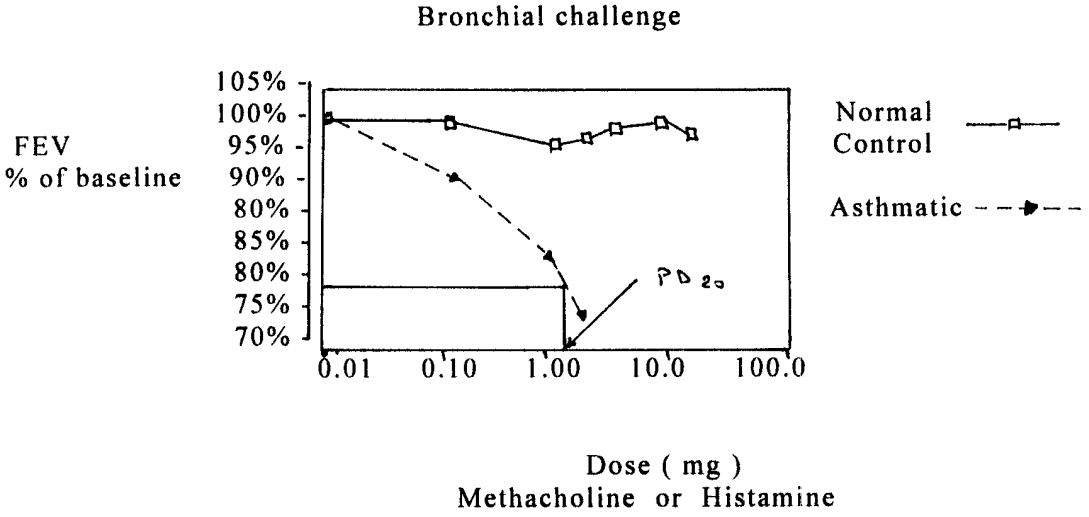


FIGURE 1: On the x-axis, the dose of challenge chemical (which could be either methacholine or histamine) is indicated in logarithmic fashion. On the y-axis, the FEV_1 after each challenge dose is plotted for an asthmatic and a normal control subject. The provocative dose that results in a 20% fall in FEV_1 from baseline is labeled the PD_{20}.

BHR is highly associated with atopy but not in a direct causal relationship (Varpela et al., 1978). Peat compared two groups of Australian school children, one living in a dry temperate inland region with high levels of grass and weed pollen, and the other group living in a humid coastal town whose major allergen was dust mites. They found a similar frequency of atopy in each group but more BHR in the area with the pollen (Peat et al.,

1987). The risk of BHR was increased in children who were allergic to both pollens and dust mite, and the severity of the BHR increased with the severity of the atopy (based on the number of positive skin tests and the size of the reactions). Risk factors for BHR developing included a family history of asthma, atopy, and early respiratory illness (Peat et al., 1987).

BHR is also more common in infants and young children (Montgomery et al., 1990). In fact, most normal infants who have been studied can be shown to react to methacholine at low doses (Tepper, 1987). BHR is increased in older individuals who smoke but not in younger smokers (Cockcroft et al., 1983; O'Conner et al., 1989). It is increased in some subjects with chronic bronchitis (Enarson et al. , 1987), allergic rhinitis (Townley et al., 1976), chronic obstructive lung disease (Yan et al., 1985), cystic fibrosis (VanAsperen, Mellis, 1981) and bronchiectasis (Varpela et al., 1978). Furthermore, BHR can be increased briefly by viral upper respiratory infections (Empey et al., 1976), exposure to ozone (Holtzman et al., 1983), nitrous oxide (Orehek et al., 1976), irritants (Brooks et al., 1995) and some occupational chemicals (Lam et al., 1979) even in some normal individuals.

When tests of nonspecific BHR are applied to general populations, the correlation is less clear between clinical asthma and bronchial hyperreactivity (Josephs et al., 1989; Backer et al., 1991). Studies that compare current symptoms and presence of BHR have found that up to 42% of currently symptomatic asthmatic subjects may not have BHR at the time they are studied (Pattemore et al., 1990). On the other hand, as many as one third of subjects with documented BHR are asymptomatic and do not appear to merit the diagnosis of asthma (Sears et al., 1986; Spiropoulos et al., 1986; Pattermore et al., 1990). This leads to the conclusion that although BHR is definitely

associated with asthma, there is enough disparity that BHR and asthma should not be considered to be synonymous and tests for BHR should not be considered diagnostic tests for asthma (Tattersfield, Higgins, 1988). Furtheremore, although a correlation exists between severity of asthma and degree of BHR, there is enough individual variation that measures of BHR cannot be used to gauge response to treatment (Josephs et al., 1990).

Early and Late Phase Allergic Reaction:

The bronchial response to inhaled antigen has been used as a model to study airway events. When allergic subjects inhale an antigen to which they are sensitive, bronchoconstriction occurs within a few minutes. This early response is due to mast cells releasing their mediators. Cells retrieved from airways by BAL shortly after antigen challenge reveal many degranulated mast cells. There is rapid release of histamine and other mediators including PGD_2. A measurable decrease in air flow is caused by constriction of bronchial smooth muscle with some airway edema (O'Byrne et al., 1987). This response is brief and usually subsides within 1 hour. This is the early phase response to allergen. In many subjects the reaction stops here. If bronchial reactivity is measured before and after this early response, it is unchanged. The early phase reaction alone does not increase BHR.

In some subjects, more frequently in children than adults, the inflammatory response continues to amplify, producing a decrease in airflow 3 to 8 hours after the initial reaction. An influx of eosinophils occurs with mucosal edema, microvasculature leak, and smooth muscle constriction. BAL shows an increase in eosinophils, macrophages, and some sloughing of epithelial cells (Gleich, 1990). Measures of air flow

usually return to normal within 12 to 18 hours after the antigen exposure. However, the airways maintain an increased responsiveness to bronchoconstrition from nonspecific stimuli that may last for several days (O'Byrne et al., 1987). This late phase reaction has been used to study the cellular and biochemical events in asthma and is used to test the function of many of the drugs used to treat asthma. This late phase reaction produces a picture that is similar to chronic asthma because it is less responsive to bronchodilators, has more BHR, and may require corticosteroid therapy to control (Smith, 1993).

Diagnosis of asthma

History:

Because asthma represents a constellation of symptoms, a definitive diagnosis may be difficult to make, especially early in the course of the illness. The infant who wheezes only with a viral respiratory infection may not go on to develop what we consider asthma, even if he wheezes with a few subsequent viral infections (Godfrey, 1985; Wilson, 1989). However, 40% to 50% of children with severe wheezing from viral infections in infancy have repeated episodes of wheezing through-out childhood (Pullan, Hey, 1982; McConnochie, Roghman, 1984) and many have increased reactivity to exercise and histamine when tested at age 8 or 9 (Moq, Simpson, 1982; Murray et al., 1992).

Recurrent symptoms of cough, wheeze, shortness of breath, and sputum production suggest asthma. Because wheeze is a symptom of intrathoracic airway obstruction, other conditions can result in wheezing. An improvement of 10% to 20% or greater in FEV_1 after inhalation of bronchodilator is a classic indicator of asthma. In some cases, this improvement cannot be

demonstrated until vigorous treatment has occurred. Other times it may be necessary to demonstrate a 20% fall in FEV_1 after exercise, inhalation of methacholine, or other challenge maneuvers. In the child who is too young to perform pulmonary function tests, the clinical history becomes the only means of diagnosing asthma. Asthma should be strongly suspected in children who experience recurrent pneumonias or "chronic bronchitis" (Taussig et al., 1981; Eigen et al., 1982).

Chronic bronchitis lasting more than 6 weeks and often persisting after a viral upper respiratory infection is a major indicator of asthma in childhood (Corrao et al., 1979; Cloutier, Loughlin, 1981). Many of these children never wheeze; others have classic symptoms of wheezing later in the course of the disease. Children with cough-variant asthma may show decreased spirometry and reversibility with bronchodilators. Many but not all will show evidence of airway hyperreactivity to methacholine challenge (Galvez et al., 1987). Response to asthma treatment, either bronchodilators or anti-inflammatory drugs, is the best diagnostic indicator of cough-variant asthma (Johnson, Osborn, 1991).

Although asthma has been divided into categories of intrinsic (nonallergic) and extrinsic (allergic) asthma, these classifications are not very useful. Both allergic and nonallergic groups are triggered by so many stimuli and respond to similar medications that is more helpful to take a "trigger" history.

The following is a discussion of some of the major trigger factors in childhood asthma:

Infections:

One of the most common precipitants of asthma in any age group is a viral respiratory infection. Viruses have been isolated

in up to 50% of episodes of wheezing in children and 20% in adults (Pattemore et al., 1992). The most common viruses that trigger wheezing are respiratory syncytial virus, rhinovirus, parainfluenza, and influenza (Pattemore et al., 1992). The more severe the respiratory infection the more likely it is to trigger wheezing in a susceptible host. The reason that viral infections are such potent triggers of asthma is believed to be their capacity to increase inflammation in the airways (Bardin et al., 1992). Damage to airway epithelium leads to enhanced BHR and, furthermore, respiratory viruses can decrease beta-adrenergic receptor function (Bjornsdottir, Busse, 1992).

Although bacterial infections rarely cause a flare in asthma symptoms, the exception to this is sinusitis, which is increasingly recognized as a significant trigger of asthma (Rachelefsky et al., 1984). This condition may be subtle, presenting with nasal congestion and cough as the only symptoms suggesting sinusitis. Sinusitis appears to exacerbate asthma in some children, although the exact mechanism whereby it accomplishes this is unknown. However, treating the sinusitis often results in much more manageable asthma (Slavin, 1991).

A bacterial infection that has gained recognition as a potential trigger of wheezing is Chlamydia pneumoniae. It has recently been implicated as a frequent cause of lower respiratory infections (as high as 9% in children under 5 years old and 19% of children 5 to 16 years old) (Hammerschlag, 1992). Several reports of wheezing associated with C. pneumoniae infection including one in which C. pneumoniae was isolated in 17% of children aged 5 to 15 who presented with acute exacerbations of wheezing have been documented (Hahn et al., 1991; Hammerschlag, 1992).

Exercise:

Eighty to ninety percent of children with asthma experience bronchospasm with exercise (Siegel, Rachelefsky, 1985).

The classic way to induce exercise asthma is to have the subject run or bicycle vigorously enough to bring the heart rate up to 80% of maximum. Exercise at this level is continued for 6 minutes and stopped. Longer duration of exercise may result in the child "running through" his asthma and thus missing it. FEV_1 or PEFR is measured at intervals and compared with pre-exercise levels. The flow rates fall within 3 to 8 minutes after terminating exercise. A positive test is a drop of 10% to 20% in FEV_1 or PEFR (Anderson, 1988) (The exact decrease in FEV_1 that is necessary to qualify for a diagnosis of exercise-induced asthma (EIA) varies from report to report, although many prefer a decrease of 20% in FEV_1 or PEFR or 25% in FEF_{25-75})

The response to exercise can be variable. Temperature and humidity affect the response: dry cold air is more asthmogenic. The type of exercise and the intensity of exercise make a difference. Free running and cross-country skiing are more likely to produce asthma, whereas swimmimg is least likely. The response to exercise may vary from day to day, and a negative exercise test does not rule out the presence of asthma. Some investigators believe that a positive response to exercise is a more reliable diagnostic test for asthma than a positive inhalation challenge test with methacholine or histamine. The mechanism of EIA is thought to be due to water loss during hyperventilation with transient hyperosmolarity of periciliary fluid and a temperature decrease in the mucosa, triggering mediator release and bronchoconstriction (Anderson, 1988). EIA need not be a cause of restricted activity. In recent years, as

many as 6% to 11% of the U.S. Olympic Team athletes have been documented to have exercise-induced bronchospasm (Pierson, 1991).

Allergens:

After the age of 2, inhalant allergens become more important in triggering asthma (Zimmerman et al., 1988). One study estimates that 95% of subjects who have asthma developed before age 40 have at least one positive immediate skin test to an inhalant allergen compared with only 25% who first have asthma developed after the age of 40 (Barbee et al., 1985). A child can have a positive skin test to an allergen without necessarily having that allergen induce a clinical response (Bardana, 1992). However, with a positive skin test the potential to respond is there. The severity of asthma attacks and the likelihood of experiencing daily symptoms of asthma increase with the number of positive skin tests. The dust mite is the major allergen provoking asthma, followed by alternaria, and cat (Peat, Woolcock, 1991). Pollens, other molds, animal dander also may be important (Bush, 1992). Foods are a rare cause of asthma (Cockcroft, 1988). In infancy, foods may be a cause of some wheezing episodes, especially in the context of an anaphylactic-type reaction, but infections are the most common trigger.

Irritants:

By far the most significant irritant exposure in childhood asthma is smoke from tobacco (Halken, 1991). Passive smoking leads to increased symptoms of cough, wheezing, more severe asthma episodes, and increased BHR. Over an extended period of time it can cause decreased lung growth and function (Murray,

Morrison, 1986; Evans et al., 1987; Martinez et al., 1988; Murray, Morrison, 1988; Young et al., 1991).

Because of the introduction of energy conserving construction methods, there are fewer air exchanges in newer homes, leading to higher levels of indoor air pollution (Samet et al., 1987). Smoke from burning wood is an irritant both indoors and outdoors. The major culprit is the fine particulate matter. Gas cooking stoves release nitrous oxide as their major pollutant. Both have been associated with higher frequency of respiratory illness and wheezing (Melia et al., 1977; Honicky et al., 1985). Outdoor pollution is also a potential source for triggering asthma. Sulfur oxide is the major irritant for asthmatic subjects, although ozone is the most prevalent pollutant. Sulfur oxide exposure can result in increased BHR and decreased pulmonary functions (Pierson, Koening, 1992). Exercise conducted in air pollution is especially conductive to increasing BHR.

Gastroesophageal reflux (GER):

The relationship between GER and asthma is complex, especially because drugs as theophyllin lower the esophageal sphincter tone, predisposing to reflux. Evidence that GER can trigger asthma and other respiratory symptoms exists (Berquist et al., 1981; Orenstein, Orenstein, 1988). Of note, in adults with undiagnosed chronic cough presenting to pulmonologists, reflux was found to be the third most common cause (Irwin et al., 1990). In a surprising number of these cases (43%), there were no other symptoms suggesting reflux besides the cough. The mechanism whereby GER induces asthma is unclear but may involve heightened bronchial reactivity (Davies et al., 1983; Herve et al., 1986). When a child has asthma resistant to medical management, especially with nocturnal exacerbations, even in

the absence of overt reflux symptoms, consider a search for GER. Monitoring of esophageal pH and a therapeutic trial of reflux medication may be the best approach (Ornestein, Ornestein, 1988).

Drugs:

Aspirin:

Aspirin and the nonsteroidal anti-inflammatory drugs can trigger asthma in children. The onset of the bronchospasm may be insidious, starting 1 to 2 hours after the drug is ingested so that the cause-and-effect relationship may be lost in the history. The incidence of aspirin-induced asthma is lower when history alone is used (1.9% to 5%), and rises when oral challenge techniques are used (up to 13% to 19%) in both children and adults
(Settipane et al., 1972; Shatz et al., 1988). The mechanism of aspirin-induced asthma is related to the inhibition of the cyclooxygenase pathway and so there is virtually 100% cross-reactivity with other nonsteroidal anti-inflammatory drugs (Barnes, Thomson, 1988). Acetaminophen is usually considered a safe alternative, but there have been rare cases of asthma triggered by this (Guidelines 1, 1991). Most aspirin-sensitive asthmatic patients can also tolerate salsalate, propoxyphene, narcotics, and pentazocine. Tartrazine had been reported to cause asthma in some aspirin-sensitive subjects (Vedanthan et al., 1977; Spector et al., 1979). More recently this has been shown to be an artifact of challenge technique caused by the very labile airways in aspirin-sensitive asthmatic patients (Stevenson et al., 1986). Tartrazine rarely, if ever, is a trigger of asthma, although it may occasionally flare urticaria in patients with chronic

urticaria. Asthmatic reactions from other azo and nonazo dyes occur with even less frequency (Stevenson et al., 1986).

Beta Blockers:

Beta-blocking drugs can trigger bronchospasm in asthmatic subjects. The effect is less with the more selective $beta_1$ – blockers but can still occur, depending on the beta-blocker and the sensitivity of the patient (Barnes, Thomson, 1988). Some patients are so sensitive that topical administration of beta-blocker eye drops has caused severe bronchoconstriction. Beta-blockers should be avoided in all patients with obstructive lung disease (Barnes, Thomson, 1988).

Angiotensin Converting Enzyme (ACE) Inhibitors:

ACE inhibitors cause cough in up to 20% of patients treated for hypertension. Whether bronchospasm is associated with this class of drugs is not yet clear (Barnes, Thomson, 1988).

Food additives and sulfites:

Sulfites:

Sulfiting agents are used to preserve foods. They can provoke asthma in as many as 4% of asthmatic subjects and 8% of corticosteroid-dependent asthmatic subjects (Taylor et al., 1988). The concentration and availability of sulfites on salad greens made salad bars a particular hazard for the sulfite-sensitive individual, causing sudden severe asthmatic reactions. By law, sulfites are now banned from salad bars. However, they are still used in some foods including processed potatoes, shrimp, lemon juice, dried fruit, beer and wines. The only way to confirm a suspected diagnosis is to cautiously undertake an oral challenge with capsules or acidified sulfur dioxide (Bush, Taylor, 1986).

There are no blood or skin tests. The cause of the reaction is believed to be airway irritation resulting from the release of sulfur dioxide, but there may also be other mechanisms involved. Sulfites contained in injectable materials such as epinephrine or local anesthetics do not cause reactions because of the small amounts involved. However, sulfites contained in some bronchodilator solutions (i.e., Bronkosol; Sanofi Winthrop Pharmaceutical, New York) are present in high enough concentrations to trigger bronchospasm in a sensitive subject (Simon, 1984).

Benzoates:

Benzoates are used as preservatives in foods. They have been demonstrated to flare urticaria in as many as 15% of children with chronic urticaria (Supramaniam, Warner, 1986). In a study of children with perennial asthma, when challenged openly, 11 of 46 had positive reactions. However, when these 11 were rechallenged in a double-blind placebo-controlled protocol, there were only three reactions confirmed (Jacobsen, 1991). It would appear that some asthmatic subjects react to benzoates, but this not a very frequent problem.

Monosodium Glutamate (MSG):

MSG can cause symptoms of the Chinese restaurant syndrome (CRS) with headache, burning sensation in the neck, chest tightness, nausea, and sweating within a few hours of ingestion in many subjects. Two types of asthmatic reactions have been reported. In one type, asthma appears within 1 or 2 hours after ingestion often associated with CRS. The other type appears 10-12 hours after ingestion and usually the patient does not have symptoms of CRS. Either reaction may be quite severe,

occasionally requiring mechanical ventilation (Allen et al., 1987). The reaction is dose related.

Endocrine factors:

Frequent reports of asthma increasing premenstrually have been documented (Gibbs et al., 1984). The cause for this has not been established. Pregnancy will more often leave an asthmatic patient unchanged or worse rather than improve the condition (Shatz et al., 1988). Thyrotoxicosis has been associated with increased severity of asthma, possibly caused by altered metabolism of hydrocortisone (Settipane et al., 1972).

Weather:

Asthma is often aggravated by weather factors independent of wind, temperature, air pollution, or pollen. Thunderstorms are particularly frequent triggers of asthma (Packe et al., 1983; Khot et al., 1988; Beer et al., 1991).

Psychological factors:

The acts of crying and laughing apart from the emotional content can trigger asthma, possibly by a reflex mechanism, or as a type of EIA. It is well accepted that there is no particular personality type that is predisposed to develop asthma. However, children with asthma are not immune from psychiatric disturbances, which have been estimated to afflict up to 12% of the general population (Mrazek, 1988). Furthermore, having to cope with a chronic disease can create a variety of psychologic problems (Mrazek, 1992). The affective type of psychiatric conditions, especially depression and anxiety disorders, occur

with a higher frequency in the more severe asthmatic patients, especially those who are corticosteroid-dependent (Mrazek, 1988). When these are present, they represent a significant risk factor for potentially fatal episodes of asthma (Strunk et al., 1985). Coexistent psychiatric disorders may contribute to poor compliance with treatment regimens and delayed recognition and response to increasing severity of asthma. How a child and his family cope with asthma may affect the outcome of asthma management (Kinsman et al., 1977). There is some evidence that in atopic families, where a child is already at risk for developing asthma, poor parenting techniques may contribute to increasing the already increased risk (Mrazek et al., 1991).

Past Medical History:

Past medical history may reveal factors that are important in evaluating a child for asthma.
Previous surgery or concomitant medical conditions such as cystic fibrosis, GER, and sickle cell disease can affect the approach to treatment.
The review of systems gives a further opportunity to seek associated symptoms that are often seen with asthma. This would include symptoms suggestive of nasal allergies such as itching, sneezing, congestion, and rhinorrhea, cough and halitosis suggestive of sinusitis, and the presence of a chronic pruritic rash suggesting atopic dermatitis. Symptoms not associated with asthma, such as failure to thrive and malabsorption symptoms, may suggest additional or alternative diagnoses (Smith, 1993).

The family history can be very helpful in suspecting the diagnosis of asthma. Although asthma and allergies are inherited separately, asthma tends to occur in a setting of a positive family history. Noting that there is a positive family history may

strengthen the suspicion that a symptom such as cough is actually asthma (Sibbald et al., 1980).
Studies have shown that 20% to 30% of the population has a strong genetic predisposition for atopy (Casolaro et al., 1996).

The environmental history should include information concerning the age and size of the family home, the type of heat and air-conditioning, and the nature of carpeting, particularly in the child's bedroom. When inquiring about pets, ask where the animals stay in the home. Pets may stay outside continuously or be limited to the basement. In some homes, the animal may sleep in the child's bedroom, often even in the bed with the child. Because animal allergens can persist for years after removal of the animal, also inquire about previous pets in the home. Because a child spends more hours in the bedroom than anywhere else, knowledge of its contents is important. Dust catchers such as stuffed animals or books may be reservoirs of dust mites. Infestations of a home with cockroaches, rats or mice may also contribute to the allergen load. Knowledge about the day care environment, school environment, and any routine activities such as after school jobs or sports activities is relevant. Always inquire about a history of cigarette smoke exposure in all the child's environments. Keep in mind that some children begin smoking before adolescence. In divided families, obtain information about all the homes that the child stays in (Smith, 1993).

Physical examination:

The physical examination in an asymptomatic asthmatic subject may be entirely normal. Stigmata of associated upper respiratory allergies or nasal obstruction, such as a transverse line across the bridge of the nose, bluish discoloration under the

eyes, swollen boggy nasal mucosa, cobblestoning (Hyperemic lymphoid follicles) in the posterior pharynx, and serous otitis media, may be noted. Signs of atopic dermatitis may also be noted.

The examination of the chest may not reveal wheezes, even when the FEV_1 is decreased. In fact, the entire physical examination may be normal when measurable obstruction is present. An increased anteroposterior diameter of the chest is often associated with chronic air trapping and suggests chronically undertreated asthma.

During symptomatic asthma, evaluation of the quality of breath sounds, use of accessory muscles of respiration, and estimation of the work of breathing are important. When asthma is severe, often the child will be unable to speak in sentences. The presence of pulsus paradoxus is associated with severe asthma. Pallor is frequent, although cyanosis is rare. When wheeze cannot be heard in a child who is struggling to breathe, "the silent chest" suggests very severe airway obstruction. Irritability, diaphoresis, tachycardia, central cyanosis, and coma are late findings in severe obstruction of the airways (Smith, 1993).

Laboratory Evaluation:

The total eosinophil count is frequently elevated in asthma, and the degree of elevation has been shown to correlate with the severity of asthma (Horn et al., 1975). Levels of 500-1000/cmm is usual in asthma. Diurnal variation in eosinophil count (increased late at night), seasonal variation (increased during periods of allergen exposure), and suppression with corticosteroids are common. Concurrent infection will reduce the eosinophil count and can be associated with leucocytosis and a shift to immature cells.

Serum IgE levels are frequently elevated in extrinsic asthma, especially in children and in conjunction with atopic dermatitis or with upper respiratory allergy. However, there is an overlap of IgE values between atopic and normal persons. Serum IgE determinations are of particular help to diagnose and monitor effects of therapy of bronchopulmonary aspergillosis, which commonly has significantly elevated serum IgE levels.

Radio-allergosorbent test (RAST) which is used to measure allergen- specific IgE concentration.

Skin tests for immediate hypersensitivity. The direct introduction of an antigen into the skin of a patient provides a simple and efficient techniques for determining IgE antibodies to specific antigens. The clinical significance of positive (wheal-and-flare) reactions depends on correlation with the history, physical findings, and other laboratory tests.

The principal indication for skin testing is a reasonable suspicion that a specific allergen or a group of allergens is producing symptoms in an allergic patient. Skin tests should be undertaken with allergens to which the patient has a probability of exposure. Exposure to pollens demonstrates regional variation: house dust mites, molds, and animal dander are relatively ubiquitous. Several suppliers provide allergens for both diagnosis and treatment as concentrated solutions or in dilutions if ordered by the physician. Individual antigens are available for epicutaneous (prick) and intradermal testing.

Interpretation of the clinical relevance of positive or negative skin tests requires correlation of the history, physical examination and other laboratory studies. Important guidelines for correct interpretation include the following: 1) Skin tests are

usually more reliable for diagnosing atopic sensitivity in patients with allergic rhinosinoconjunctivitis than in patients with asthma (many asthmatic patients who have positive skin tests cannot relate their symptoms physically or temporally to known allergen exposure or may not react to provocation challenges). 2) Skin testing with mixes of allergens is less reliable (due to the multiple allergens in the mixes effectively diluting each other and thus leading to false-negative results) than with specific allergens, but mixes containing fewer than 10 antigens can be useful for screening purposes, especially in small children. Further testing with individual allergens may still be required if negative test results do not correlate with clinical history or if clinical suspicion warrants. 3) Positive skin tests correlate highly when the suspected manifestation of food allergy is acute urticaria, angioedema, or anaphylaxis. The negative predictive value of skin testing for food allergy (i.e., a negative test truly representing a lack of allergic reactivity to that antigen) is substantially greater than the positive predictive value because of the high incidence of false-positive test responses. For these reasons in many cases of suspected food allergy (nonanaphylaxis) with positive skin tests, a double-blind placebo-controlled oral food challenge with reproduction of symptoms is necessary in order to make a diagnosis of true food allergy. 4) Correlation of positive skin tests with causative factors in atopic dermatitis is usually unreliable but may correlate in some instances with ingested, inhaled, or topical allergen challenge. As with other suspected manifestations of food allergy, a double-blind placebo-controlled oral food challenge may be required to establish the diagnosis. A positive double-blind placebo-controlled oral food challenge may be found in up to one-third of children with atopic dermatitis. 5) The use of skin tests to diagnose immediate hypersensitivity to

drugs is limited because metabolites of the drug in question, not the drug itself, are usually responsible. These metabolites are usually unknown or unavailable. Skin testing with complete protein drug allergens (e.g., insulin or animal serum) and penicillin (which has been extensively studied) provides useful information.

Sputum analysis. If the child can produce it, sputum can be clear or mucopurulent, yellow or greenish sputum can result from eosinophil or cellular debris and does not always imply infection. Sputum in extrinsic asthma usually shows 25%-35% ciliated columnar epithelial cells, 5%-8% eosinophils, and a varying amounts of polymorphonuclear leucocytes (PMNs). In intrinsic asthma or chronic bronchitis the sputum composition is similar, with a preponderance of PMNs and eosinophils in range of 5% - 20%. When intrinsic asthma worsens, the ratio of PMNs to eosinophils usually remains the same, with an increase in total cell count; in extrinsic asthma, worsening is usually accompanied by an increase in total eosinophil count. Corticosteroid therapy will depress the total eosinophil count, a response that can be used to assess the adequacy of the dosage.

Secondary infection in association with an increase in PMNs and an increased PMN-eosinophil ratio; microorganisms may also be noted. Sputum culture and sensitivities are indicated to establish further the presence and cause of infection, especially in patients with persistent or refractory symptoms.

Cytologic evaluation of the nasal secretions may also show neutrophils suggestive of sinusitis or eosinophils suggestive of, but not diagnostic, for allergic rhinitis.

Tuberculin test. It is important to know the status of tuberculin sensitivity in the asthmatic patient, especially if corticosteroid therapy is anticipated.

Arterial blood gases. Arterial PO_2 (PaO_2) is often decreased, even in asymptomatic asthma, as a result of maldistribution of airflow in relation to pulmonary blood flow. At times, PaO_2 may be normal, but alveolar- arterial oxygen difference is abnormally widened (>20mm Hg). Acute attacks of asthma are accompanied by further impairment in oxygenation, as indicated by decreases in PaO_2 that are proportional to the severity of the obstruction of flow. Conversely, acute attacks of asthma are often associated with hyperventilation (decreased $PaCO_2$), the magnitude of which is inversely proportional to the severity of the attack. Therefore, mild attacks may result in considerable hyperventilation, and severe attacks may result in little or no hyperventilation or even hypoventilation ($PaCO_2$>42 mm Hg). Consequently, the presence of an elevated or even normal $PaCO_2$ in a dyspneic patient during an attack of asthma indicates a severe degree of obstruction and the need for aggressive therapy and frequent monitoring of arterial blood gases.

Arterial blood gases should be obtained in any patient who exhibits features of severe acute asthma (marked dyspnea, relative resistance to bronchodilator drugs, tachycardia, signs of hyperinflation, use of accessory muscles of respiration, suprasternal retractions, and pulsus paradoxus), especially if there is any disturbance of consciousness. If significant hypoxemia (PaO_2< 60 mm Hg) and/or a normal or elevated $PaCO_2$ are present, vigorous therapy, including supplemental oxygen, is required, and arterial blood gases need to be monitored serially to ascertain the adequacy of arterial oxygenation, alveolar ventilation, and tissue perfusion.

Arterial pH is usually normal or slightly alkaline during asthmatic attacks of mild to moderate severity due to the accompanying hypocapnia (respiratory alkalosis) with or without metabolic compensation through renal bicarbonate loss. However, in severe asthma (FEV_1 <15-20% predicted), varying degrees of acidemia may occur as a result of metabolic acidosis (base excess <-2 mEq/liter) (due to lactic acid accumulation) with or without accompanying respiratory acidosis ($PaCO_2$ >42 mm Hg) (due to alveolar hypoventilation). Metabolic (lactic) acidosis is probably secondary to 1) the markedly increased work of breathing associated with severe airflow obstruction and hyperventilation, and 2) tissue hypoxia due to reduced venous return (and reduced cardiac output) associated with hyperinflation and arterial hypoxemia (Lawlor, Tashkin, 1995).

Radiology:

A chest x-ray film should be taken during the initial evaluation of asthma.
This is more to rule out the presence of other conditions that could be present rather than to prove the diagnosis of asthma. Air trapping may be present, even in asymptomatic children. Atelectasis is frequently present in acute asthma. Whether a chest x-ray film should be obtained with each acute episode is controversial. It is most reasonable to base this decision on the clinical picture (Ellis, 1988).

Consideration should be given to obtaining a sinus film in children who are symptomatic with cough and asthma, especially if nasal obstruction is present. In cases where no obvious reason exists for a flare of asthma, consider checking for sinusitis (Ellis, 1988). In some cases a CT scan of the sinuses may be necessary to document the presence of sinusitis.

Spirometry:

Pulmonary function testing does not make a diagnosis but places a disease into physiologic categories. Interpretation first categorizes a patient as having either obstruction to air flow or restriction of lung volume. A diagnosis can then be made by combining these categories and correlating them to the clinical history and examination. Asthma is an obstructive process, characterized primarily by low flows with normal volumes. Restrictive lung disease is characterized by small volumes with normal flows.

The spirometry tests generally used are forced vital capacity, FEV_1, the ratio of FEV_1 to forced vital capacity, and FEF_{25-75}. In obstructive pulmonary disease, flow and timed volumes decrease. The FEV_1 decreases as less air is exhaled in the same amount of time. The FEF_{25-75} mostly evaluates the smaller airways after much of the initial air from central airways is already expelled. A reduction in this value occurs with small airway obstruction in asthma. In more severe obstruction, forced vital capacity decreases as air trapping increases residual volume, but the flow is still relatively low for the reduced lung volume. That is, the ratio of FEV_1 to forced vital capacity is decreased in asthma (Mueller, Eigen, 1992).

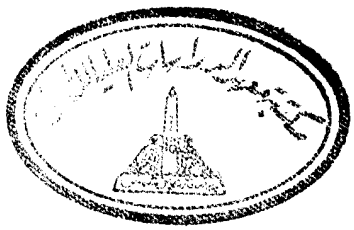
Documenting that the spirometry is normal, or how abnormal it is, and what kind of response is present to inhaled bronchodilators, are a part of staging the asthmatic patient (Guidelines 1, 1991). Most children aged 6 and older can perform spirometry with some coaching. When following up a child with asthma, it is important to obtain measures of lung function when the child is absolutely well. This helps establish the predicted range for this individual child. The published

predicted values for FVC, FEV_1 and FEF_{25-75} are valid, but there is a wide range of "normal" from 80% to 120%. An FEV_1 value of 82% of predicted, although still within the "normal" range could represent substantial obstruction in a child who is capable of attaining values of 140% of predicted. When FVC and FEV_1 are in the normal range, a decrease in the FEF_{25-75} suggests there is obstruction present in the smaller airways. This is often present in asymptomatic children (Smith, 1993).

Peak Expiratory Flow Rate

The peak flow meter measures one parameter of lung function: the fastest air flow rate. This is a test of large airway function and is highly effort dependent. This device can be used by some coordinated 2- and 3-year old children and many 4 and 5 year olds who cannot yet perform the spirometric maneuver. The guidelines for the treatment of asthma from the NIH use monitoring of peak flow as part of the routine management of asthma, especially for children who have moderate to severe asthma or when the asthma is unstable or labile (Guidelines 1, 1991). The use of home peak flow meter monitoring has now come to be a standard part of asthma management in most children with asthma (Cross, Nelson, 1991).

Home peak flow monitoring can provide information that documents the presence or absence of changes in air flow that may suggest asthma. There is a normal circadian rhythm in peak flow, with the lowest occurring early in the morning and the peak in late afternoon. The difference between the high and low values should be far less than 20% normally (Quackenboss, Lebowitz, 1991). Although the peak flow is a very effort-dependent measurement, it can provide an objective index of lung function that is currently unavailable in any other manner.



For the best results, instruct the patient carefully in the proper use of the peak flow meter. It should be held properly. If the fingers cover any of the air holes, false values will result. This instrument measures the rate of air flow when it is at its fastest, or peak, which occurs early in expiration. The child should inhale as deep as possible and then exhale as forcefully as possible. The maneuver is a quick expiratory burst as opposed to the complete expulsion of a full breath used in spirometry. It is important to obtain at least three good maneuvers. Record the best value, not an average. When monitoring daily PEFR, the measurement obtained immediately after getting out of bed in the morning, before medication, gives a good indicator of events during the previous night (Bellia et al., 1988). A measurement taken 15 minutes after inhaled bronchodilator gives an indication of the magnitude of response to bronchodilator. It is the premedication PEFR that should be used to determine morning to evening variability. At a minimum, prebronchodilator measurements should be obtained in the morning and the evening. If the child is taking regular inhaled bronchodilators, pretreatment and 15- to 30-minute post treatment readings should be obtained. Ideally pretreatment and post-treatment measurements three times per day would give an optimal snapshot of the day's function for many families.

These measurements provide important data on the status of the asthma condition on a day-to-day basis (Clark et al., 1992). An important value to ascertain is the "best ever" value. Unlike the predicted values for FVC and FEV_1 the predicted values for the PEFR should not be derived from a chart of predicted values based on the age or height of the child. There is far more variability in expected peak flow rates. The best way to find the "best ever" peak flow value for a child is by observation of the peak flow record for a 2- to 4-week observation period when the

child is asymptomatic. This value should not be looked for on the initial visit when the peak flow meter is introduced. It is impossible to determine whether the child is performing the maneuver to the best of his or her ability. Often, after a few days of use, the values begin to increase some. When the child returns for a follow-up visit, it is a good idea to have a demonstration of how the child performs the maneuver and records the values. On occasion, the "best ever" value will only be ascertained after a period of maximal treatment, including corticosteroids. Once this value is determined, it can be used to establish treatment guidelines for home management of the asthma. As the child grows, or improvement in the asthma evolves, this value will increase. A variety of schemes are used to evaluate the PEFR information. One of the most clever uses a stop light analogy (Mendoza, 1991). The green zone is 80% to 100% of the "best ever" value and the desired goal of treatment. Optimally, PEFR readings will be in the green zone before bronchodilator use and remain there continuously. Values between 50% and 80% of "best ever" are in the yellow or warning zone. Readings in this area denote inadequate control of asthma. Readings under 50% of "best ever" fall in the red zone. This is the alert zone where intervention is essential. These ranges are arbitrary, and tighter ranges may be necessary for some asthmatic patients who are extremely labile. Care must be taken to ensure that the test is reliably performed and accurately recorded. A wide area exists for errors to creep in. Confabulation and inadequate techniques are possibilities. Despite this, properly performed peak flow measurements provide useful information for the management of many asthmatic children (Twarog, 1991)

Complications

(Smith, 1993):

Infection can occur secondary to an acute or chronic asthmatic attack or can precede asthma symptoms and precipitate an attack. Respiratory infections commonly initiate wheezing in both childhood and adult asthma. Young children are particularly prone to the development of wheezing with "colds", which frequently is the early presentation of asthma. Any child who has repeated chest colds and bronchitis should be suspected of having asthma.

1-Viral respiratory infections alone are the principal types implicated in provoking asthma attacks. Respiratory syncytial virus, parainfluenza, influenza, rhinovirus and adenovirus are the most common and probably act by directly triggering the hyperactive airway of the asthmatic patient, although other mechanisms have been suggested, including virus-specific IgE antibody, virus-induced beta-adrenergic subsensitivity, and virus-enhanced mediator release.

2-Bacterial infections are not usually involved in precipitating attacks, with the exception of bacterial sinusitis. Recurrent attacks or persistent episodes of asthma are often associated with chronic sinusitis (discussed in full details later). Mycoplasmal agents are also often associated with exacerbations of asthma.

3-Pneumonia can occur secondary to an asthma attack, usually when attacks are persistent, with increased mucus accumulation and mucus plugging. Viral pneumonia is most common under the age of 5 years. Mycoplasma pneumonia is most common from 5 – 30 years, and bacterial pneumonia especially pneumococcal, is most common after 30 years.

Atelectasis. Lobar, segmental, or subsegmental atelectasis can occur in both acute and chronic asthma, usually secondary to bronchial obstruction with mucus plugs. Atelectasis should be suspected in the patient who has worsening or persistence of cough, wheezing, dyspnea, or fever following a course of therapy, especially when the findings of localized, reduced breath sounds and dullness to percussion. Atelectasis of the right middle lobe is common and can go undetected in an asymptomatic patient. The diagnosis of atelectasis is substantiated by chest x-ray. Atelectasis is most common in young children and frequently recurs at the same site.

Pneumothorax and pneumomediastinum

Pneumothorax is an uncommon complication in acute asthma. Recurrence in the same patient suggests the presence of some other anatomic abnormality (e.g., pulmonary bleb or cyst, congenital lobar emphysema). Repeated or violent coughing or intermittent positive pressure breathing (IPPB) can precipitate pneumothorax. The latter should be suspected if there is a sudden development of pleuritic chest pain associated with dyspnea, tachypnea and occasionally, cough. Pneumothorax is confirmed by chest x-ray. A small pneumothorax (<25%), if unassociated with severe dyspnea or chest pain, may be allowed to resolve spontaneously with bed rest. Most patients with pneumothorax have a lung collapse greater than 25% and are best treated with closed thoracostomy and water-seal drainage with or without suction.

Pneumomediastinum and subcutaneous emphysema, usually involving the neck and clavicular area, are more common than pneumothorax. They are usually asymptomatic and are detected as an incidental finding on chest x-ray or soft-tissue swelling or

a crunching sound on skin pressure about the neck and chest. A crunching sound on auscultation over the heart (Hamman's crunch) indicates mediastinal emphysema. Pneumomediastinum and subcutaneous emphysema can be precipitated by vigorous coughing or by the use of a positive-pressure breathing apparatus. Pneumomediastinum can present with substernal pain and, in more severe cases, dyspnea, tachypnea, tachycardia, hypotension, and cyanosis, especially over the upper body. Most patients require no treatment, but in patients with severe disease (cardiovascular and respiratory compromise), needle aspiration or mediastinostomy is necessary.

Bronchiectasis rarely occurs in asthma; when it does occur, it is usually associated with concomitant chronic bronchitis, persistent atelectasis, chronic infection, or allergic bronchopulmonary aspergillosis. Chronic cough, purulent sputum, and hemoptysis are frequent symptoms. Digital clubbing, which does not occur in uncomplicated asthma, is suggestive physical finding. The diagnosis can sometimes be made by chest x-ray but usually requires tomography or computerized axial tomography and, in rare instances, bronchography.

Bronchopulmonary aspergillosis is an overgrowth by and hypersensitivity to the organism Aspergillus fumigatus. It occurs primarily in adult asthmatic patients.

Cardiovascular complications. Arrhythmias are the most common cardiovascular complication in asthma and vary from occasional premature ventricular contractions to severe or fatal ventricular arrhythmias. Arrhythmias are more common in asthmatic patients with underlying cardiac disease and are aggravated by

hypoxemia and the excessive use of adrenergic drugs. Right heart strain can occur during an acute asthma attack, but right heart failure is rare except in the presence of prolonged severe hypoxemia and fluid overload. Pulmonary hypertension may occur during an acute asthma attack, but cor pulmonale is rare unless it is associated with chronic bronchitis, emphysema, or both.

Status asthmaticus and respiratory failure

Status asthmaticus is severe asthma unresponsive to the usual methods of treatment, including beta-adrenergic aerosols, subcutaneous epinephrine, intravenous aminophylline and initial corticosteroid therapy. Status asthmaticus is associated with a 1-3% mortality; it should be treated, therefore, as a life-threatening medical emergency. It is precipitated by the same factors as those that may provoke an attack of asthma and include exposure to an allergen or primary irritant, viral respiratory tract infection, change in ambient temperature or humidity, an emotional crisis, gastric acid aspiration, poor compliance in taking prescribed medication or poor access to medical care. Often, there may be no obvious initiating factor.
Some historic features strongly suggest that a patient is approaching status asthmaticus including:

* Change in the pattern of symptoms, including increasing frequency and severity of attacks of dyspnea and wheezing, progressive exertional intolerance and cough that has become productive of scantier amounts of tenacious sputum, which may be discolored.

* Refractoriness to bronchodilator drugs that, despite more frequent use and even abuse, result in a lesser magnitude and duration of effect.

* Personality changes, including increasing anxiety and irritability and at times panic.

* History of recent and frequent repeated episodes of severe asthma treated either in the emergency room and/or hospital with only short-lived benefit.

The physical findings include the following:

* An anxious patient with tachypnea and obviously labored breathing interfering with speech.

* Suprasternal retractions, use of accessory muscles of respiration (especially the sternocleidomastoids) and signs of hyperinflation (low diaphragms, decreased lateral excursions of the chest, hyperresonance).

* Diminished breath sounds, expiratory prolongation, and wheeze heard on both inspiration and expiration. When obstruction is very severe, however, there is little air movement and flow rates are too low to generate a wheeze, so that wheezing can be absent ("silent chest").

* Paradoxical pulse (>10 mm Hg decrease in systolic blood pressure during inspiration). Suprasternal retractions and pulsus paradoxus are frequently present (~ 50%) when the FEV_1 is less than 1.0 liter in adults but are rarely present when the FEV_1 is greater than 1.25 liters.

* Evidence of increased sympathoadrenal activity, including tachycardia, increase in systolic blood pressure and diaphoresis.

Differential Diagnosis

The differential diagnosis for the child with wheezing can be approached on an age-related basis (Table 1).

Infants are at higher risk for congenital abnormalities and some infectious conditions, whereas older children may have inflammatory or psychogenic conditions more often. Conditions

such as aspiration of a foreign body, cystic fibrosis and gastroesophageal reflux (GER) may occur in any age group. Any aspect of the history that is atypical for asthma, such as a history of sudden onset of symptoms, coughing or wheezing with feedings, neonatal requirement for ventilatory support, or symptoms of stridor, may suggest the need to pursue additional diagnostic tests.

Table 1: Differential Diagnosis of Asthma

Infants	
Bronchopulmonary dysplesia	Gastroesophageal reflux
Laryngotracheobronchomalacia	Congenital heart disease
Immunodeficiency syndrome	Chronic respiratory infection
Laryngotracheobronchitis	Chlamydia, respiratory
Congenital malformation (Vascular ring, Tracheoesophageal fistula)	syncitial virus, adenovirus, pertussis)
Cystic fibrosis	
Foreign body	
Children and adolescents	
Foreign body	Habit cough
Cystic fibrosis	Laryngeal dysfunction
Gastroesophageal reflux	Bronchiectasis
Laryngotracheobronchitis	Alpha - antitrypsin deficiency
Croup	Mechanical obstruction
Ciliary defects	(lymph nodes, etc.)
Vasculitis syndromes (Churg-Strauss)	

Hyperventilation

(Ellis, 1988; Neddenriep et. al., 1989; Bierman, Pearlman, 1990)

On the other hand, a positive family history for allergic diseases and asthma and normal growth and development, combined with a history of intermittent cough and/or wheeze, tend to support the diagnosis of asthma. Because asthma is so common, it is important to realize that it may coexist with other conditions listed in Table 1 (Smith, 1993).

Suspicion of the possibility of alternative or additional diagnoses should be sustained when the history is atypical or the response to good medical management is suboptimal.

Vocal cord dysfunction may masquerade as asthma (Christofer et al., 1983). These patients may wheeze and experience dyspnea of such a severity that they are treated as severe asthmatic patients with high-dose corticosteroids and even mechanical ventilation. Characteristically they appear to be refractory to usual asthma treatment. The presumed mechanism is an abnormal adduction of the vocal cords during inspiration particularly, and occasionally, during inspiration and expiration. Flow volume curves show a flattened inspiratory curve. Blood gases are usually normal, but occasionally the severity of the glottic closure can result in hypoxemia. The appearance of the larynx and the flow volume curves are normal between symptomatic episodes. The best way to make the diagnosis is by direct observation of the cords through a rhinoscope during an attack. This condition can not be produced voluntarily. It is believed to be a type of conversion reaction and is treated with psycotherapy and speech therapy (Goldman, Muers, 1991). On occasion, both asthma and vocal cord dysfunction coexist and present an incredibly difficult diagnostic problem. Spirometry, blood gases,

laryngoscopy and occasionally tests for bronchial hyperreactivity may be necessary to clarify the diagnoses.

Another condition that is important in the differential diagnosis of asthma is the hyperventilation syndrome. It can be mistaken for asthma. Symptoms typically include shortness of breath with difficulty breathing, sighing, and chest pain, often with paresthesias of the face and extremities, dizziness, or even loss of consciousness (Fanurik et al., 1991). Blood gases during the episode will show a normal to elevated pO_2 with a respiratory alkalosis compared with acute asthma, which will have a decrease in pO_2. If an asthmatic subject also has hyperventilation syndrome, it can trigger an asthma attack or occur during an attack and render it much more difficult to treat.

Prognosis

Some studies suggest that the major prognostic factor determining whether wheezing persists into adolescence and adulthood is not the age of onset of disease but the presence of persistent symptoms in childhood (Weiss et al., 1980; Kelly et al., 1987). Park, in the British National cohort study, found that 21% of all children had at least one episode of a wheezing illlness by age 5 (Park et al., 1986). Of those who only had one episode by age 5, 8% had symptoms at age 10. Among those who had more than 10 episodes of wheezing before age 5, 38% had symptoms at age 10.

Gerittsen in the Netherlands studied asthmatic subjects from childhood to adulthood over a 16 years period (Gerritsen et al., 1989). He found that 57% became asymptomatic.

However, 14% of the adults who considered themselves asymptomatic had spirometric evidence of significant obstruction of which they were completely unaware. Eighty-three percent of

the symptomatic children and 58% of symptomatic adults had evidence of BHR. Those who had less BHR when initially studied, were more likely to "outgrow" their symptoms.

Kelly, in the Melbourne asthma study, found that by age 21, 50% of those who had mild intermittent episodes of wheezing in childhood were wheeze free, and most of the others had trivial symptoms (Kelly et al., 1988). Of note, about 61% of those who were asymptomatic at age 21 still had evidence of BHR and by age 28, one third of these had recurrence of symptoms. Kelly found the degree of BHR tended to parallel asthma severity, but so much overlap existed that he could not reliably match BHR with severity. Ninety-five percent of those with persistent asthma in childhood were still wheezing at age 21. A disturbing factor was the finding of a steeper decline in FEV_1 from age 7 to age 28 in the group with the most severe asthma compared with those with less severe asthma. These subjects retained their ability to reverse with bronchodilator but as a group had poorer lung function.

Reports of inadequate treatment of these asthmatic subjects were disturbing. Seventy five percent of those with frequent episodes of asthma and 40% of those with persistent asthma were believed to be receiving inadequate treatment for their asthma (Martin et al., 1982). Fifty percent with frequent asthma and one third with persistent asthma did not regard overuse of inhalers as potentially dangerous. Other studies have documented underdiagnosis and undertreatment of asthma (Speight et al., 1983; Clifford et al., 1989; Croner et al., 1992).

Treatment of asthma

General Overview

The approach to asthma management encompasses nonpharmacologic and pharmacologic issues. This disease is chronic. There is no currently known cure. Many who believe they are no longer symptomatic actually have persistent obstruction. Often misconceptions exist about the nature of asthma and its treatment. Because of its episodic nature, a requirement for continuous medication use needs to be explained. Parents are often shocked when an asthma death is reported by the news media. The general perception is that asthma is a trivial nuisance rather than a potentially life-threatening disease. The frequent disparity between patient and physician recognition of symptom severity versus actual physiologic function measured by objective tests leads to under treatment. Communicating with the patient and the family regarding the nature of asthma and the reason for the treatment recommendations is crucial. Writing out the treatment plan eliminates problems with memory and facilitates compliance.

The goals of therapy for each patient should be specifically discussed to achieve the following:

1- Maintain normal activity levels
   A. Regular school attendance.
   B. Full participation in physical education and recreational activities.
2- Prevent episodic flares
   A. Eliminate nocturnal symptoms.
   B. No emergency room visits or hospitalization.
3- Avoid adverse side effects of drugs.
4- Maintain normal pulmonary function (Smith, 1993).

The treatment plan will usually include a mixture of treatment modalities. Avoidance of specific trigger factors, pretreatment

when avoidance is not possible, and environmental control measures when indicated are fundamentals of good treatment. The medications used should be the minimum necessary to control the current condition. Written guidelines should be given delineating the day-to-day management, as well as measures to take for flares in the condition. These guidelines should be individualized to the asthmatic child's specific condition and past history of exacerbations.

Nonpharmacolgic Treatment

Avoidance Techniques. Avoidance of factors that can trigger or aggravate asthma is one of the major tenets of good asthma management. An exception to this is exercise. Most children with asthma can and should participate in school and elective athletic endeavors with appropriate pretreatment. It is the exceptional asthmatic patient who needs to be excluded from regular physical activity. All asthmatic patients, allergic or nonallergic, may experience exacerbation of symptoms by irritants such as cigarette smoke, wood burning stoves, air pollution, strong odors, and sprays. Health care providers should recommend that parents and other caretakers not to smoke in the home or in the car around the child. Although they may be unable to stop smoking, parents can control where they smoke. Emphasizing how harmful cigarette smoking is on each follow–up visit reinforces this. A switch to heating sources other than wood burning devices may be impossible, but every effort should be made to render these as safe as possible. Families should try to eliminate aerosols in the home: cooking, cleaning, and personal hygiene products. On days with high air pollution, encourage the child to remain indoors. If that is not possible, try to limit exercise performed outdoors at this time (Smith, 1993).

Allergens may be very important triggers of asthma in the allergic child. Pollens and outdoor mold spores cannot easily be avoided. Closing windows and using an air conditioner will help keep these outside allergens from coming in the house. Opening windows on cool nights should be avoided.
Indoor allergens are somewhat more manageable. The major indoor allergens are dust mites, animal emanations and mold. Allergen elimination techniques may be costly, not only financially but emotionally. Recommendations should be based on a reasonable estimate of the importance of the allergen in triggering symptoms in each individual patient. Information on extensive environmental control measures is available (Platts-Mills, 1992).

Worldwide, house dust mites are the major allergen triggering asthma (Van Bever, Stevens, 1989). Because a decrease in the mite level has been shown to decrease asthma symptoms and BHR, efforts in this area may be very rewarding (Platts-Mills, et al., 1982; Murray, Ferguson, 1983; Schober et al., 1992).
Dust mite precautions include the following:
1- Encasing mattress, box springs, pillow in airtight covers.
2- Washing bedding weekly in hot water (T> 130).
3- Keeping indoor humidity between 40% and 50%.
4- Remove carpets (especially if laid on concrete).
5- Consider:
   A- Using of chemical agents to kill mites or alter the antigen.
   B- Pet elimination or washing of pet.
   C- Air filtration units (central or room type).

A pet in the home can be a major source of allergens. Animals can spread not only their own allergens but also dust mite,

pollens and molds that adhere to the coat. The most effective way to decrease animal allergen in the home is to remove the pet completely. Even then it may take months of vigorous cleaning to reduce the allergen load (Woods et al., 1989). Often the family resists this. A compromise would be to keep the animal only outside or at least always out of the bedroom. No cats or dogs are "hypoallergenic". The length of the hair is not relevant because the allergen is in the dander (dogs) and sebaceous gland material and saliva (cats). Some animals elaborate less allergen than others, this may explain why some patients report being able to tolerate certain animals better than others. This trait is not species-specific, and the reasons for it are not known. Any warm-blooded animal may be allergenic. Even if the skin test to a particular animal is negative, an allergic family should be cautioned against obtaining a pet because sensitization is likely to be acquired with prolonged exposure. It is easier not to introduce a pet into the exposure to get it out again.
Weekly washing of a cat can significantly decrease the release of antigen. Furthermore, the presence of a carpet in a room with a cat results in more than 100 times the accumulation of allergen. Washing the cat, removing the carpets, cleaning regularly, and using an air filtration unit can result in allergen levels low enough to allow some cat-sensitive patients to live in the same house with a cat (DeBlay et al., 1991).

Recommendations concerning air cleaning devices are somewhat controversial. Room air cleaning devices with a high-efficiency particulate air (HEPA) filter have been demonstrated to be effective against particles that remain airborne, such as animal emanations, mold spores, and cigarette smoke (Reisman et al., 1990). Because dust mite allergen is heavier and only airborne when the room air is disturbed, these devices may be

less effective as mite control agents. Units that filter air for a central heating unit are more problematic. Factors such as volume of air moved, cleanliness of the air ducts, and type of filtering device are important. In general, less data exits to substantiate the effectiveness of these units (Nelson et al., 1988).

Allergen Immunotherapy. In the allergic asthmatic patient, allergen immunotherapy may be a consideration. This therapy has been shown to be effective in reducing symptoms of asthma and reducing BHR (Aas, 1971; Ohman, 1989). The first approach should always be environmental control and medical management. If an allergen is regarded as a significant provoking factor, cannot be avoided, and use of medications is deemed excessive, a risk benefit analysis may indicate that immunotherapy should be considered. Over 3 to 5 years it will decrease response to the allergen. Studies performed on efficacy of immunotherapy to cats and dogs have been performed in environments without household exposure to the animals. Heavy exposure to an animal, such as sleeping with it, may render immunotherapy less successful (Dykewicz, 1992).

Immunotherapy with allergen should not be undertaken in an asthmatic patient whose condition is not stable. An injection should not be given if FEV_1 or peak flow is less than 70% of the child's best ever (Bousquet et al., 1990). Because worsening asthma can be a reaction to immunotherapy, the asthmatic subject should be closely monitored when receiving immunotherapy. Asthmatic subjects have a higher risk for severe or fatal anaphylaxis than nonasthmatic subjects (Lockey et al., 1987). All patients receiving immunotherapy, but especially asthmatic patients, should be observed after the injection for at least 20 to 30 minutes in a location where a physician and

emergency equipment are immediately available (Norman, VanMetre , 1990).

Relaxation and Control of Emotional Factors, especially at the onset of or during an acute attack, may help abort or relieve symptoms. To be effective this requires education and practice during symptom-free periods. Since panic is a definite component of any attack and tends to increase the respiratory rate and aggravate bronchospasm, patients should be trained to relax their breathing.
The following instructions are helpful: Cease activity and relax. Take slow, deep breaths. Place one hand on the upper abdomen to determine expansion (diaphragmatic movement). Inhale through the nose, letting the abdominal area expand (instead of the upper chest). Slowly exhale through pursed lips (as though blowing out a candle), allowing the abdominal muscles to relax.
The following positions will enhance relaxation and abdominal breathing (which ever suits the patient):

1) Sitting in a chair
   a) First position. Lean forward, resting the elbows on the knees.
   b) Second position. Lean forward over a table, resting the shoulders, arms, and head on a pillow placed on the table. When short of breath for a prolonged period, one can sleep in this position.
2) Standing
   a) First position. Stand facing a wall, about 12–18 inches away, with the forearms resting against the wall. Rest the head on the forearms, and put one foot forward in a stepping position to relax abdominal muscles.

b) Second position. Lean with the back against a wall, with the feet about 12 inches from the wall and the knees and trunk slightly bent.

The patient should be encouraged to practice relaxed breathing exercises frequently during symptom-free periods (Lawlor, Tashkin, 1995).

Fluid Therapy is important to prevent or treat dehydration and thereby reduce the viscosity of mucus and enhance expectoration. Instruct asthmatic patients to increase fluid intake even during symptom-free periods. Oral fluids should be increased at the start of symptoms and continued unless vomiting is aggravated. More severe attacks are usually associated with some degree of dehydration because of reduced fluid intake and increased fluid loss resulting from hyperventilation, sweating, and/or vomiting. In such instances, especially in unresponsive attacks and status asthmaticus, intravenous fluid therapy is indicated. Volumes and rates of fluid administration vary with the extent of dehydration; attention should be given to possible overload (i.e., pulmonary edema), especially during prolonged treatment (Lawlor, Tashkin, 1995).

Postural Drainage with Chest Percussion and Vibration is helpful in mobilizing and facilitating expectoration of mucus in patients with acute attacks of asthma complicated by significant atelectasis, mucus plugging, or pneumonia. These measures can also be useful in the chronic asthmatic patient with thick or copious sputum. The procedure is usually well tolerated in patients with moderate symptoms but may aggravate wheezing in more severe attacks. Patients often notice improvement about 30 minutes after these procedures, but if instead symptoms worsen, the procedures should be discontinued. Postural drainage is best

accomplished after periods of recumbency (e.g., morning awakening) and may be repeated 2 – 3 times a day, depending on need. Postural drainage should be preceded by inhalation of a nebulized or pressurized bronchodilator.

The patient is placed in various chest-dependent positions to permit gravity drainage of secretions. For 1–2 minutes, a therapist applies percussion with cupped hands over the chest area to be drained. The patient is encouraged to breathe slowly and deeply. In individual patients, particular positions are chosen or emphasized based on clinical or radiographic evidence of retained secretions.

These maneuvres are contraindicated in patients with hemoptysis, pneumothorax or convulsions (Lawlor, Tashkin, 1995).

Oxygen is indicated for acute attacks in which hypoxemia is pronounced (documented clinically or by monitoring arterial oxygen saturation or arterial blood gases).

Oxygen must be fully humidified and can be administered by nasal cannula, face mask, or Venturi mask. Small children who do not tolerate nasal cannulas or face masks may require tents; however, in tents, oxygen levels are more difficult to maintain and monitor.

Administer oxygen at low flow rates, usually 2–4 liters/ minute, trying to maintain the arterial PO_2 level between 70 and 100 mm. Hg. Hypoventilation secondary to oxygen therapy may occur in hypercapneic patients, but this is more common in patients with chronic obstructive pulmonary disease than in others.

Pharmacologic Therapy

According to the Expert Panel Report 2 " Guidelines for the Diagnosis and Management of Asthma" from the American National Institutes of Health Publication (1997):

* Underdiagnosis and inappropriate therapy are major contributors to asthma morbidity and mortality.
* Goals of asthma therapy are:
• Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning or after exertion).
• Maintain (near) "normal" pulmonary function.
• Maintain normal activity levels (including exercise and other physical activity).
• Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations. Provide optimal pharmacotherapy with minimal or no adverse effects.
• Meet patients' and families' expectations of and satisfaction with asthma care.
• Persistent asthma is most effectively controlled with daily anti-inflammatory therapy.
• A stepwise approach to pharmacologic therapy is recommended:
- The amount and frequency of medication is dictated by asthma severity and directed toward suppression of increasing airway inflammation.
- Initiate therapy at a higher level at the onset to establish prompt control and then step down.
- Continual monitoring is essential to ensure that asthma control is achieved.
- Step-down therapy cautiously once control is achieved and sustained.
- Step-down therapy is necessary to identify the minimum

medication necessary to maintain control.
- Regular follow-up visits (at 1- to 6- month intervals) are essential to maintain control and consider appropriate step down in therapy.
• Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal asthma control.
• At each step, patients should be advised to avoid or control allergens, irritants, or other factors that make the patient's asthma worse.
• Medications are now categorized into two general classes: long-term-control medications used to achieve and maintain control of persistent asthma and quick-relief medications used to treat acute symptoms and exacerbations. It is emphasized that the most effective medications for long-term therapy are those shown to have anti-inflammatory effects.
• New medications are available- long-acting inhaled beta2-agonists, nedocromil, zafirlukast, montelukast and zileuton- that have positions in therapy for long-term control and prevention of symptoms.
• There is an increased understanding of inhaled cortico-steroids and their significant role in asthma therapy.

Long-Term-Control medications

Long-term-control medications are taken daily on a long-term basis to achieve and maintain control of persistent asthma. They include anti-inflammatory agents, long-acting bronchodilators, and leukotriene modifiers. Because eosinophilic inflammation is a constant feature of the mucosa of the airways in asthma, the most effective long-term-control medications are those that

attenuate inflammation (Kerrebijn et al., 1987; Haahtela et al., 1991; van Essen-Zandvliet et al., 1992).

Corticosteroids

Corticosteroids are the most potent and consistently effective long-term-control medication for asthma. Their broad action on the inflammatory process may account for their efficacy as preventive therapy. Their clinical effects include reduction in severity of symptoms, improvement in peak expiratory flow and spirometry, diminished airway hyperresponsiveness, prevention of exacerbations, and possibly the prevention of airway wall remodeling (Jeffery et al., 1992; Barnes et al., 1993). Which of these clinical effects depend on specific anti-inflammatory actions of corticosteroids is not yet clear. Corticosteroids suppress the generation of cytokines, recruitment of airway eosinophils, and release of inflammatory mediators. These anti-inflammatory actions of corticosteroids have been noted in clinical trials and analyses of airway histology (Busse, 1993; Booth et al., 1995).

Early treatment with systemic corticosteroids has been shown to decrease the need for hospitalization and emergency room care (Harris et al., 1987; Chapman et al., 1991). The onset of action is gradual, starting within 3 hours and peaking at 6 to 12 hours after administration. If high-dose (in the range of 1 to 2 mg./kg. prednisone or equivalent) corticosteroid treatment is started early, short bursts of 5 to 10 days may be all that is necessary during an acute exacerbation. Adverse effects of short bursts of corticosteroids include increased appetite and weight gain, fluid retention, rounding of the face, mood alterations, hypertension, reversible alteration in glucose metabolism, and aseptic necrosis of head of femur (Guidelines 2, 1997).

If a short burst of corticosteroids is used, tapering the dose is not necessary because of potential adrenal suppression. However, a tapering dose may lessen side effects that some experience from the abrupt withdrawal of corticosteroids. Also, it allows a slightly longer treatment interval so one can assess the clinical results of the corticosteroid withdrawal.

If the symptoms do not resolve, continued treatment is indicated. This should always be combined with maximal asthma therapy including pharmacologic and nonpharmacologic maneuvers. During some severe exacerbations, patients may even require a divided dose therapy at doses as high as 1 to 2 mg./ kg. given twice daily to control the symptoms (Zeiss, 1992).

An alternate-day regimen or inhaled corticosteroids should be considered in those requiring continuous daily corticosteroids. However, alternate-day therapy or inhaled therapy alone should not be introduced until daily therapy has controlled the symptoms. When using alternate-day corticosteroid therapy, a short acting form such as prednisone, prednisolone, or methylprednisolone should be used. With continuous corticosteroid treatment, either daily or alternate day, any tapering program should be conducted based on therapeutic response. If asthma flares or a deterioration in the PEFR is seen, introduce higher dose daily corticosteroids until a remission is obtained. Then return to the last dose (daily or alternate day) at which the patient was very stable. Do not attempt to treat flares with a higher alternate-day dose. The taper can be resumed when the patient is again stable. If the asthma flares every time a taper is attempted, the child should be considered steroid dependent at this time and should be maintained at a dose that keeps him stable while the asthma management program is reevaluated. There may be an underlying trigger that can be dealt with or other nonsteroidal treatment measures may be introduced. If a

child requires repeated short bursts of corticosteroids at monthly or every other month intervals, this child's condition is not stable and requires reevaluation.

If continuous oral corticosteroids are necessary, there may be a significant risk of osteoporosis, hypertension, cataracts, myopathy, hypothalamic-pituitary-adrenal axis suppression, and Cushing's syndrome. The lowest possible dose should always be sought.

The metabolism of corticosteroid drugs can be affected by concomitant administration. For example, phenytoin or carbamazepine speed metabolism of corticosteroids. Methylprednisolone appears to be more sensitive to drug-drug interactions than prednisolone or prednisone. Some patients may fail to absorb or metabolize some glucocorticosteroid preparations efficiently (Szefler S.J., 1991).

Inhaled Corticosteroids.

Inhaled corticosteroids are the most effective long-term therapy available for patients with persistent asthma. In general, inhaled corticosteroids are well tolerated and safe at the recommended dosages (van Essen-Zandvliet et al., 1992; Barnes, 1995). Systemic effects have been identified, particularly at high doses (see Table 2 for a definition of high-, medium- and low-dose inhaled corticosteroids), but their clinical significance remains unclear. Furthermore, there may be interindividual variations in dose-response effects, and thus some patients may experience effects at lower doses. In general, the potential for adverse effects must be weighed against the risk of uncontrolled asthma; to date evidence supports the use of inhaled corticosteroids, especially at low and medium doses.

Local adverse effects

Oral candidiasis (thrush) is one of the most common adverse effects of inhaled corticosteroids. Positive throat cultures of

Table 2: Estimated comparative daily dosages for inhaled corticosteroids for children

Drug	Low Dose	Medium Dose	High Dose
Beclomethasone diproprionate 42 mcg./puff 84 mcg./puff	84–336 mcg. (2–8 puffs) (1-4 puffs)	336–672 mcg. (8-16 puffs) (4-8 puffs)	> 672 mcg. (> 16 puffs) (> 8 puffs)
Budesonide DPI: 200 mcg./dose	100-200 mcg.	200-400 mcg. (1-2 inhalations)	> 400 mcg. (>2 inhalations)
Flunisolide 250 mcg./puff	500-750 mcg. (2-3 puffs)	1000-1250 mcg. (4-5 puffs)	>1250 mcg. (>5 puffs)
Fluticasone MDI: 44, 110, 220 mcg./puff DPI: 50, 100, 250 mcg./dose	88-176 mcg. (2-4 puffs-44 mcg.) (2-4 inhalations-50 mcg.)	176-440 mcg. (4-10 puffs-44 mcg.) OR (2-4 puffs-110 mcg.) (2-4 inhalations-100 mcg.)	>440 mcg. (>4 puffs-110 mcg.) OR (>2 puffs-220 mcg.) (>4 inhalations-100 mcg.) OR (>2 inhalations-
Triamcinolone acetonide 100 mcg. / puff	400-800mcg. (4-8 puffs)	800-1200 mcg. (8-12 puffs)	>1200 mcg. (>12 puffs)

Metered-dose inhaler (MDI) dosages are expressed as the actuater dose (the amount of drug leaving the actuater and delivered to the patient). This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, all of which is not available to the patient. Dry powder inhaler (DPI) doses are expressed as the amount of drug in the inhaler following activation (from the Guidelines 2, 1997).

Candida can be identified in about 45% to 58% of patients, whereas clinical thrush is diagnosed in only 0% to 34% of patients (Shaw, Edmunds, 1986). With lower dosages of inhaled corticosteroids, candidiasis is uncommon (5%) (Rinehart et al., 1975), although it is more frequent in adults than in children. Prevention and treatment: Use a spacer/holding chamber to reduce the incidence of colonization and clinical thrush, rinse mouth with water after inhalation (Seltroos, Halme, 1991) and administer inhaled corticosteroids less frequently (b.i.d. versus q.i.d.). Topical or oral antifungal agents should be used to treat active infections.

* Dysphonia is reported in 5% to 50% of patients using inhaled corticosteroids and is associated with vocal stress and increasing dosages of inhaled corticosteroids (Toogood et al., 1980). Prevention and treatment: Use of a spacer/holding chamber, temporarily reduce dosage, or rest for vocal stress.

* Reflex cough and bronchospasm can be reduced by slower rates of inspiration and/or use of a spacer/holding chamber or pretreatment with an inhaled beta$_2$-agonist. There is no convincing evidence that the routine use of an inhaled beta$_2$-agonist prior to each dose of inhaled corticosteroids increases intrapulmonary delivery of the inhaled corticosteroid or reduces dosage requirement.

Systemic adverse effects

* Linear growth: The potential effects of inhaled corticosteroids on children's growth are important because the drugs are more likely to be used for longer periods of time, although it is recognized that poorly controlled asthma itself may result in

retarded linear growth. Growth in children with asthma who have not received any form of corticosteroid therapy may be influenced by concomittant atopy, asthma severity and being male among other factors (Kamada, Szefler, 1995; Allen, 1996).

Indeed, childhood asthma appears to be associated with delayed maturation and a longer period of reduced growth prior to puberty. Although this could be viewed as growth suppression, these delays do not appear to compromise the attainment of final predicted adult heights (Balfour-Lynn, 1986; Allen, 1996).
Because of these numerous confounding factors, evaluating the effects of systemic or inhaled corticosteroids on growth in children with asthma has been challenging and has led to contradictory findings.

A few studies of children with asthma have identified some growth delay in those treated with inhaled corticosteroids, suggesting that some caution may be prudent until this important issue can be studied further. A 1-year controlled trial comparing children with mild-to-moderate asthma receiving either inhaled beclomethasone (400 mcg. per day, administered without spacer /holding chamber) or oral theophylline demonstrated slower growth in children receiving beclomethasone (Tinkelman et al., 1993). In a placebo-controlled, community-based 7-month study of 7-to 9-year-old children to determine the effect on growth during treatment with beclomethasone at 400 mcg./day, growth was significantly decreased in both males and females, and there was no evidence of catch-up growth during a 5-month washout period (Doull et al., 1995). However, the results of this short-term study may not reflect effects on long-term growth.

A recent meta-analysis of the influence of inhaled beclomethasone in the attainment of expected adult height did not find any significant adverse effects regardless of dose, duration of asthma, or disease severity (Allen et al., 1994). An

uncontrolled follow-up study (mean duration of 2.7 years, range of 1 to 5 years) or prepubertal children with moderate asthma found no effect of inhaled budesonide (800 mcg. mean daily dose) on long term growth (Ninan , Russel , 1992). A majority of studies do not demonstrate a negative effect on growth with dosages of 400 to 800 mcg. a day (Wolthers, 1996; Kamada et al., 1996).

* Bone metabolism/Osteoporosis: The few published observations regarding the effect of inhaled corticosteroids on bone metabolism and osteoporosis are complicated by oral corticosteroid use and small patient populations (Jennings, 1991a, 1991b). The effects of inhaled corticosteroid on markers of skeletal metabolism – serum osteocalcin, serum alkaline phosphatase, and urinary hydroxyproline: creatinine ratio – are equivocal (Hodsman et al., 1991). The clinical implications in terms of risk of osteoporosis and fracture after long-term use of inhaled corticosteroids are still unknown (Jennings et al., 1991b). Although low and medium dosages of inhaled corticosteroids appear to have no major adverse effects on any clinically important measure of bone metabolism (Toogood et al., 1991; 1995), a dose-dependent, yet significant, reduction in bone mineral content of subjects with asthma has been associated with inhaled corticosteroid use (Packe et al., 1992). Elderly female patients may be more at risk due to preexisting osteoporosis, previous use of oral corticosteroids, a sedentary lifestyle, and the normal changes of estrogen in aging that affect calcium utilization. However, the risk of uncontrolled asthma, which may unnecessarily limit the patient's mobility and activities, must be weighed against the limited risks of using inhaled corticosteroids. Prevention and treatment: Concurrent treatment

with calcium supplements and vitamin D (and estrogen replacement where appropriate) is reasonable.

* Disseminated Varicella: Although high doses of inhaled corticosteroids theoretically present risks similar to those of systemic corticosteroids, the reports of disseminated varicella in patients receiving only inhaled corticosteroids are rare, causality is not clear, and there is no evidence that recommended doses of inhaled corticosteroids are immunosuppressive. Cases have been reported of children with severe persistent asthma on immunosuppressive doses of systemic corticosteroids developing fatal disseminated disease from varicella infection (Kasper, 1990). Other case reports indicate complications for patients with Strongyloides or tuberculosis who take high doses of systemic corticosteroids. Prevention and treatment: Children who require episodic therapy with systemic corticosteroids who have not had clinical varicella should receive the varicella vaccine. The vaccine should not be administered to patients who are receiving immunosuppressive doses of systemic corticosteroids (2mg./kg. or more of prednisone equivalent or 20 mg./day of prednisone for more than 1 month), unless this dosage is discontinued for at least 1 month. Children who have completed a short prednisone course may receive varicella vaccine without delay (American Academy of Pediatrics, 1995). Children and adults on treatment with immunosuppressive doses of corticosteroids who have not been immunized against varicella and are exposed to varicella infection are candidates for zoster immunoglobulin and therapy with oral acyclovir. Should they develop clinical varicella, intravenous acyclovir with or without zoster immunoglobulin should be given.

* Dermal thinning and increased ease of skin bruising have been observed in elderly subjects treated with inhaled corticosteroids. The effect is dose dependent, but the threshold dose is variable (Capewell et al., 1990).

* Hypothalamic pituitary axis (HPA) function: The issue of inhaled corticosteroid effects on HPA function is complex and requires further study. Several studies indicate that low-to-medium doses of inhaled corticosteroids do not appear to have significant effects on HPA function (Doull et al., 1995). However, some studies showed that, compared with placebo, both beclomethasone and budesonide reduced the 24–hour urinary cortisol excretion even in doses as low as 400 to 500 mcg. daily (Tabachnik, Zadik, 1991). At higher doses, there appears to be a dose-dependent effect on different measures of HPA function (Kamada et al., 1996). Fluticasone caused greater adrenal suppression at doses of 400 to 2000 mcg. than budesonide in equivalent doses (Clark et al., 1996; Boorsma et al., 1996). The clinical significance, if any, of these findings is not known.

* Cataracts: Although cataracts are a documented adverse effect of systemic corticosteroids, there appears to be no association between inhaled corticosteroids and posterior subcapsular cataracts in adults (Toogood et al., 1993) or children (Simons et al., 1993).

* Glucose metabolism: In a study of children, inhaled corticosteroids at dosages from 400 to 1000 mcg./day (budesonide) failed to affect fasting glucose or glycated hemoglobin (Turpeinen et al., 1991). At 1000 mcg./day, a significantly greater rise in fasting serum insulin levels and

glucose during a glucose tolerance test was noted, but results remained within normal limits.

Cromolyn Sodium and Nedocromil

Although cromolyn and nedocromil have distinct properties (Clark, 1993), they have similar anti-inflammatory actions. Their mechanism appears to involve the blockade channels (Alton, Norris., 1996) and they modulate mast cell mediator release and eosinophil recruitment (Eady, 1986). They also inhibit the early and late asthmatic response to allergen challenge and exercise-induced bronchospasm (EIB) (November et al., 1994).

The two compounds are equally effective against allergen challenge (Gonzalez, Brogden, 1987) although nedocromil appears to be more potent than cromolyn in inhibiting bronchospasm provoked by exercise (deBenedictis et al., 1995), by cold dry air (Juniper et al., 1987) and by bradykinin aerosol (Dixon, Barnes, 1989).

Both compounds have been shown to reduce asthma symptoms, improve morning peak flow and reduce need for quick-relief beta$_2$-agonists (Schwartz et al., 1996). Two large clinical trials comparing nedocromil MDI 4 mg. q.i.d. to cromolyn sodium MDI 2 mg. q.i.d. demonstrated that they are generally comparable in mild allergic patients and that nedocromil was more effective than cromolyn in nonallergic patients using inhaled corticosteroids. Furthermore, nedocromil may have a modest effect in helping reduce the dose requirements for inhaled corticosteroids (O'Hickey, Rees, 1994).

Dosing recommendations for both drugs are for administration four times a day, although Nedocromil has been shown to be clinically effective with twice-daily dosing (Creticos et al.,

1995). Cromolyn MDI is 1 mg./puff, children are given 1–2 puffs t.i.d.-q.i.d. and the nebulizing solution is 20 mg./ampoule, children are given 1 ampoule t.i.d.-q.i.d.. One dose prior to exercise or allergen exposure provides effective prophylaxis for 1–2 hours.
Nedocromil MDI is 1.75 mg./puff, children are given 1–2 puffs b.i.d.-q.i.d..

Long-Acting Beta$_2$-Agonist
(Beta-Adrenergic Agonists)

The principal action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Long-acting inhaled beta$_2$-agonists have a duration of bronchodilation of at least 12 hours after a single dose (D'Alonzo et al., 1994). This class of medication is not to be used for exacerbations. Rather, it is used as an adjunct to anti-inflammatory therapy for providing long-term control of symptoms, especially nocturnal symptoms (Yates et al., 1995) and to prevent exercise-induced bronchospasm.

Salmeterol: (inhaled) MDI is 21 mcg./puff, children are given 1–2 puffs/12 hours and DPI 50 mcg./blister, children are given 1 blister/12 hours.

Albuterol (sustained-release) 4 mg. tablets, children are given 0.3–0.6 mg /kg./day, not to exceed 8 mg./day.

Methylxanthines

Theophylline, the principally used methylxanthine, provides mild-to-moderate bronchodilation in asthma. Although its mechanism of action has yet to be established (Weinberger, Hendeles, 1996), recent evidence suggests that low serum concentration of theophylline are mildly anti-inflammatory

(Kidney et al., 1995). Sustained-release theophylline may be considered as an alternative, but not preferred, long-term preventive therapy when issues arise concerning cost or adherence to regimens using inhaled medication. Monitoring serum concentration levels is essential to ensure that therapeutic, but not toxic, doses are achieved. In children, starting dose 10 mg./kg./day; usual maximum: <1 year of age: 0.2 (age in weeks) + 5 = mg./kg./day; >1 year of age: 16 mg./kg./day.

Leukotriene Modifiers

Leukotrienes are potent biochemical mediators released from mast cells, eosinophils and basophils that contract airway smooth muscle secretions, and attract and activate inflammatory cells in the airways of patients with asthma (Henderson, 1994). Three leukotriene modifiers – zafirlukast, montelukast and zileuton – have recently become available as oral tablets for the treatment of asthma.

From the information currently available, it appears that leukotriene modifiers improve lung function (Gaddy et al., 1992) and diminish symptoms and the need for short-acting inhaled beta$_2$-agonists. The majority of trials have been conducted in mild-to-moderate asthma, and the improvements noted have been modest. Leukotriene modifiers may be considered an alternative to low-dose inhaled corticosteroid therapy for patients with mild persistent asthma, although increased clinical experience and further study in a wide range of patients are needed to determine those patients most likely to benefit from leukotriene modifiers and to establish a more specific role for leukotriene modifiers in asthma therapy.

Zafirlukast, a leukotriene receptor antagonist, has been demonstrated to attenuate the late response to inhaled allergen and post-allergen induced bronchial responsiveness (Dahlen et

al., 1994) through selectively inhibiting the binding of leukotriene types D (LTD) and E (LTE) and is 1000 to 10000-fold more selective for leukotriene receptors than for alpha-receptors, beta-receptors, histamine receptors or others. It was the first drug of this type to be approved. Its dose in children is not yet established (Pharmacology Online, 1999). It is taken orally as 20 mg. tablet twice daily in adults.

Montelukast, is the second leukotriene receptor antagonist to be approved in the U.S.A.. It is taken once daily and its efficacy in children, as young as 6 years, has been demonstrated. It is found in 2 forms: 10 mg. film-coated tablet and 5 mg. chewable tablet.

Zileuton, a 5-lipoxygenase inhibitor, has been demonstrated to provide immediate and sustained improvements in FEV_1 (mean increase of 15% above placebo) in placebo-controlled trials in patients with mild-to-moderate asthma (Israel et al., 1996). Compared to placebo, the patients with moderate asthma treated with zileuton experienced significantly fewer exacerbations requiring oral corticosteroids (Israel et al., 1996), thus suggesting anti-inflammatory action. Finally, zileuton is capable of attenuating bronchoconstriction from exercise (Meltzer et al., 1996) and from aspirin in aspirin-sensitive individuals (Israel et al., 1993). Because liver toxicity has been found in some subjects receiving zileuton, it is recommended that hepatic enzymes (ALT) be monitored in patients who take this medication. Zileuton is a microsomal CYP3A4 enzyme inhibitor that can inhibit the metabolism of terfenadine, warfarin and theophylline. Doses of these drugs should be monitored accordingly. In adults, it is given either two 300 mg. tablets or one 600 mg. tablet q.i.d.. In children, dosage is still not established.

Quick-Relief Medications

Quick-relief medications are used to provide prompt relief of bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness and wheezing. They include short-acting beta$_2$-agonists and anticholinergics. Although the onset of action is slow (>4 hours), systemic corticosteroids are important in the treatment of moderate-to-severe exacerbations because they prevent progression of the exacerbation, speed recovery and prevent early relapses.

Short-acting Beta$_2$-Agonists

Short-acting beta$_2$-agonists relax airway smooth muscle and cause a prompt (within 30 minutes) increase in airflow. Inhaled short-acting beta$_2$-agonists are the drug of choice for treating acute asthma symptoms and exacerbations and for preventing EIB.

Albuterol MDI: 90 mcg./puff, dose in children: 1 – 2 puffs 5 minutes prior to Exercise.

Bitolterol MDI: 370 mcg./puff }
Pirbuterol MDI: 200 mcg./puff }dose in children: 2 puffs
Terbutaline MDI: 200 mcg./puff } t.i.d., q.i.d., p.r.n.

Albuterol Rotahaler DPI: 200 mcg./capsule, dose in children: 1 caps. q 4 – 6 hours as needed and prior to exercise.

Albuterol Nebulizer solution: 5 mg./ml. (0.5%), dose in children: 0.05mg./kg.in2–3 c.c. of saline q. 4–6 hours.

Bitolterol Nebulizer solution: 2 mg./ml. (0.2%), dose in children: not established.

Prior to 1990, many clinicians prescribed short-acting beta$_2$-agonists on a regularly scheduled basis in the belief that this treatment regimen improved overall asthma symptom control. Some recent reports, however, have modified these beliefs. For

example, in moderate asthma, regular use of a potent inhaled beta$_2$- agonist (fenoterol) produced a significant diminution in asthma control and objective measurements of pulmonary function (Sears et al., 1990). In mild asthma, regularly scheduled use of albuterol compared to use on an as-needed basis only resulted in no significant differences in a variety of outcome indices. Although regularly scheduled use of beta$_2$- agonists in mild asthma produced no harmful effects in a 4–month period, it also produced no demonstrable benefits (Drazen et al., 1996). Similar findings were noted in studies with moderate asthma (D'Alonzo et al., 1994). Based on these and other observations (Cockcroft et al., 1993; Suissa et al., 1994), the regularly scheduled, daily use of short-acting beta$_2$ -agonists is not generally recommended.

The frequency of beta$_2$-agonist use can be clinically useful as a barometer of disease activity because increasing use of beta$_2$-agonists has been associated with increased risk for death or near death in patients with asthma (Spitzer et al., 1992) The use of more than one beta$_2$-agonist canister (e.g., albuterol, 200 puffs per canister) predominantly for quick-relief treatment during a 1 –month period most likely indicates overreliance on this drug and suggests inadequate asthma control (Spitzer et al., 1992).

Anticholinergics

Cholinergic innervation is an important factor in the regulation of airway smooth muscle tone. Ipratropium bromide is a quaternary derivative of atropine that does not have atropine's side effects. Ipratropium bromide may provide some additive benefit with inhaled beta$_2$ -agonists in severe asthma exacerbations. Its effectiveness in long-term management of asthma has not yet been demonstrated (Kerstjens et al., 1992).

Ipratropium: MDI: 18 mcg./puff, dose in children: 1– 2 puffs q 6 hours

Nebulizer solution: 0.25 mg /ml. (0.025%), dose in children: 0.25–0.5 mg. q 6 hours.

Systemic corticosteroids

Systemic corticosteroids can speed resolution of airflow obstruction and reduce the rate of relapse (Connett et al., 1994).

Methylprednisolone: 2, 4, 8, 16, 32 mg. tablets, dose in children: short course "burst": 1–2 mg./kg/day maximum.

Prednisolone: 5 mg. tabs., 5 mg./5 ml., 15 mg./5 ml., dose in children: 60 mg./day, for 3-10 days.

Medications to reduce oral systemic corticosteroid dependence

Troleandomycin, Cyclosporine, Methotrexate, Gold, Intravenous Immunoglobulin, Dapsone and Hydroxychloroquine.

These regimens to reduce oral systemic corticosteroid dependence should be used only in selected patients who are under the supervision of an asthma specialist. Although some of the compounds have corticosteroid-sparing effects, their use in asthma remains complicated because of highly variable effects, potential toxicity, and limited clinical experience (Bernstein et al., 1996). Colchicine is not considered effective in reducing need for oral systemic or high doses of inhaled corticosteroids (Newman et al., 1997).

Complementary alternative medicine

Alternative healing methods are not substitutes for recommended pharmacologic therapy.

Although alternative healing methods may be popular with selected patients and of some interest to investigators, their scientific basis has not been established.

The most widely known complementary alternative medicine methods are acupuncture, homeopathy, herbal medicine, and Ayurvedic medicine (which includes transcendental meditation, herbs and yoga).

A review of multiple trials on the use of acupuncture in asthma concluded that the trials lacked quality and that the effectiveness of acupuncture in treating asthma has not been established (Kleijnen et al., 1991). One trial, however, demonstrated benefit in EIB (Fung et al., 1986). Homeopathy, based on the "law of similars" and the use of infinitesimally small doses is as yet unproven for asthma (Reilly et al., 1986); some homeopathic remedies may contain potent unidentified pharmacologic agents (Morice, 1986). No controlled clinical trials have been reported on herbal medicines, and the claims of effectiveness of western plant derivatives for asthma remain unsubstantiated (Ziment, Stein, 1993), it may be important to inquire about all the medications a patient uses and advice the patient accordingly.

Stepwise approach for managing asthma in adults and children older than 5 years of age

According to the Expert Panel Report 2 (July, 1997) the aim of asthma therapy is to maintain control of asthma with the least amount of medication and hence minimal risk for adverse effects. Control of asthma is defined as:

* Preventing chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion).

* Maintaining normal activity levels (including exercise and other physical activity).

* Preventing recurrent exacerbations of asthma and minimizing the need for emergency department visits or hospitalizations.
* Providing optimal pharmacotherapy with minimal or no adverse effects.
* Meeting patients' and families' expectations of and satisfaction with asthma care.

The stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is used to achieve this control. This is illustrated in the Table (4).

Because asthma is a chronic inflammatory disorder of the airways with recurrent excerbations, therapy for persistent asthma must emphasize efforts to suppress inflammation over the long term and prevent exacerbations. Recommendations in the stepwise approach to therapy are based on the Expert Panel's review of the literature and the Expert Panel's experience and opinion.

Gaining control of asthma

The clinician must judge individual patient needs and circumstances to determine at what step to initiate therapy. There are two appropriate approaches to gaining control of asthma:

* Start treatment at the step appropriate to the severity of the patient's disease at the time of evaluation and gradually step up if control is not achieved.

OR

* At the onset, administer therapy at a level higher than the patient's step of severity to gain rapid control. This can be accomplished by either a short course of systemic corticosteroids along with inhaled corticosteroids or initiating a medium-to-high

dose of inhaled corticosteroids. Once control is gained, step down the therapy.

The more aggressive approach of gaining prompt control with a higher level of therapy is preferred, in the opinion of the Expert Panel. At present, there are no studies directly comparing the two approaches – the traditional step-up care (low dose to high) vs. step-down-care (initial high dose to low). However, there is evidence supporting a more aggressive initial approach.

First, asthma symptoms and altered pulmonary function are related to the level of ongoing airway inflammation. Suppression of airway inflammation is more likely to occur with higher doses of corticosteroids. Furthermore, studies indicate that the dose of inhaled or systemic corticosteroids can be reduced and the clinical benefits sustained once the disease is controlled (Haahtela et al., 1994). A preliminary observation in a retrospective study of children suggests that initiating inhaled corticosteroids early in the course of the disease results in better clinical benefit and less accumulated corticosteroid dose over the long term (Agertoft, Pedersen, 1994). Therefore, it is conceivable that a more aggressive approach in initial therapy will more rapidly suppress airway inflammation, restore pulmonary function, and allow for eventual asthma control at lower doses of anti-inflammatory therapy.

Continual monitoring is essential to ensure that asthma control is achieved. Control is indicated by, for example, peak expiratory flow (PEF) values indicating less than 10 to 20% variability or PEF consistently greater than 80% of the patient's personal best, minimal symptoms, minimal need for short-acting inhaled beta$_2$-agonist, absence of nighttime awakening and no activity limitations.

If control is not achieved with initial therapy (e.g., within 1 month), the pharmacologic management plan and possibly the diagnosis, should be reevaluated.

Maintaining control of asthma

Once control is achieved and sustained for several weeks or months, a reduction in pharmacologic therapy- a step down – is appropriate and helpful to identify the minimum therapy for maintaining control. Reduction in therapy should be gradual because asthma can deteriorate at a highly variable rate and intensity.

In general, the last medication added to the medical regimen should be the first medication reduced. Although guidelines for the rate of reduction and intervals for evaluation have not been established, the opinion of the Expert Panel is that the dose of inhaled corticosteroids may be reduced about 25% every 2 to 3 months to the lowest dose possible required to maintain control. It is likely that most patients with persistent asthma will continue to benefit from daily medication to suppress underlying airway inflammation. Patients may relapse when inhaled corticosteroids are completely discontinued (Waalkens et al., 1993).

Regular follow-up visits (at 1- to 6- month intervals). Clinicians need to assess whether control of asthma has been maintained and if a step down in therapy is appropriate. Clinicians also need to monitor and review the daily self-management and action plans, the medications, and the patient's self-management behaviors (e.g., inhaler and peak flow monitoring techniques, actions to control factors that aggravate their asthma).

The Expert Panel recommends referral to an asthma specialist for consultation or comanagement of the patient if there are

difficulties achieving or maintaining control of asthma; immunotherapy is being considered; the patient requires step 4 care (step 3 or 4 care for infants and young children); or the patient has had a life-threatening exacerbation.

Pharmacologic steps

The following recommendations for pharmacologic therapy at different steps of asthma severity see Table (4) are intended to be general guidelines for making therapeutic decisions. They are not intended to be prescriptions for individual treatment. Specific therapy should be tailored to the needs and circumstances of individual patients.

Pharmacologic therapy must be accompanied at every step by patient education and measures to control those factors that contribute to the severity of the asthma.

If optimal control of asthma is not achieved and sustained at any step of care (nocturnal symptoms, urgent care visits, or an increased need for short-acting beta $_2$ -agonists are key indications that asthma is not optimally controlled), several actions may be considered:

* Patients adherence and technique in using medications correctly should be assessed.

* A temporary increase in anti-inflammatory therapy may be indicated to reestablish control. A deterioration of asthma may be characterized by gradual reduction in PEF (approximately 20 %), by failure of inhaled bronchodilators to produce a sustained response, by a reduced tolerance to activities or exercise, and by the development of increasing nocturnal symptoms. To regain control of asthma, a short course of oral prednisone is often effective. If asthma symptoms do not recur and pulmonary

functions remain normal, no additional therapy is necessary. However, if the prednisone burst does not control symptoms, is effective only for a short period of time (e.g., less than 1 to 2 weeks), or is repeated frequently, the patient should be managed according to the next higher step of care.

* Other factors that diminish control may need to be identified and addressed. These factors include the presence of a coexisting condition (e.g., sinusitis), or a new or increased exposure to allergens or irritants, patient or family barriers to adequate self-management behaviors, or psychosocial problems.

Table 3: Classification of severity of asthma

	Symptoms	Nighttime Symptoms	Lung function
STEP 4 Severe Persis-tent	*Continual symptoms *Limited physical activity *Frequent exacerbations	Frequent	*FEV_1 or PEF < 60% predicted * PEF variability >30%
STEP 3 Moderate Persistent	*Daily symptoms *Daily use of inhaled short-acting beta -agonist *Excaerbations affect activ *Exacerbations >2 times a week: may last days.	>1 time a week	*FEV_1 or PEF > 60% - <80% *PEF variability >30%
STEP 2 Mild persistent •	*Symptoms >2 times a week but <1 time a day *Exacerbations may affect activity	>2 times a month	*FEV_1 or PEF > 80% predicted *PEF variability 20 – 30%
STEP 1 Mild intermittent	*Symptoms <2 times a wk. *Asymptomatic and normal PEF between exacerbations. *Exacerbations brief (from a few hours to a few days); intensity may vary.	<2 times a month	*FEV_1 or PEF > 80% predicted *PEF variability <20%

From the Guidelines for the Diagnosis and Management of Asthma (1997)

In some cases, alternative diagnoses may need to be considered, such as vocal cord dysfunction.

* A step up to the next higher step of care may be necessary.
* Consultation with an asthma specialist may be indicated.

Intermittent asthma

Step 1: Mild intermittent asthma. Short-acting inhaled beta$_2$-agonists taken as needed to treat symptoms are usually sufficient therapy for mild, intermittent asthma. If effective in relieving symptoms and normalizing pulmonary function, intermittent use of short-acting inhaled beta$_2$-agonists can continue to be used on an as-needed basis. If significant symptoms reoccur or beta$_2$-agonists is required for quick-relief treatment more than two times a week (with the exception of using beta -agonist for exacerbations caused by viral infections and for exercise-induced bronchospasm (EIB), the patient should be moved to the next step of care.

Patients with intermittent asthma who experience EIB benefit from taking inhaled beta$_2$ -agonists, cromolyn, or nedocromil shortly before exercise.

Cromolyn or nedocromil taken before unavoidable exposure to an aeroallergen known to exacerbate the patient's asthma may be beneficial (Cockcroft, Murdock, 1987).

The Expert Panel recommmends the following actions for managing exacerbations due to viral respiratory infections, which are especially common in children. If the symptoms are mild, inhaled beta - agonist (every 4 to 6 hours for 24 hours, longer with a physician consult) may be sufficient to control symptoms and improve lung function. If this therapy needs to be repeated more frequently than every 6 weeks, a step up in long-term care

is recommended. If the viral respiratory infection provokes a moderate-to-severe exacerbation, a short course of systemic corticosteroids should be considered. For those patients with a history of severe exacerbations with viral respiratory infections, systemic corticosteroids should be initiated at the first sign of the infection.

Table 4: Stepwise approach for managing asthma in adults and children older than 5 years of age: Treatment

	Long-term control	Quick relief	Education
STEP 4 Severe Persistent	Daily medications: *Anti-inflammatory: inhaled corticosteroid (high dose) AND *Long-acting bronchodilator: either long-acting inhaled beta$_2$-agonist, sustained-release theophylline, or long-acting- beta$_2$-agonist tablets AND *Corticosteroid tablets or syrup long term (make repeat attempts to reduce systemic steroids and maintain control with high dose inhaled steroids)	*Short acting bronchodilator: Inhaled beta$_2$-agonists as needed for symptoms: *Intensity of treatment will depend on severity of exac. *Use of short-acting inhaled beta$_2$-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.	Steps 2 and 3 actions plus: *Refer to individual education/counceling
STEP 3 Moderate Persistent	Daily medication: *Either Anti-inflammatory: inhaled corticosteroid (medium dose) OR Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator specially for night-time symptoms; either	*Short-acting bronchodilator: inhaled beta$_2$-agonists as needed for symptoms. *Intensity of treatment will depend on severity of exacerbation *Use of short-acting inhaled beta$_2$-agonists on a daily basis, or increasing use, indicates need for additional long-term control therapy.	Step 1 actions plus: *Teach self-monitoring *Refer to grp. education if available. Review and update self-management plan

	long-acting inhaled beta$_2$-agonist, sustained-release theophylline, or long-acting beta$_2$-agonist tab lets. *if needed Anti-inflammatory: inhaled corticosteroids (medium-high dose) AND Long-acting broncho-dilator, especially for nighttime symptoms; either long-acting inhaled beta$_2$-agonist stained-release theo-phylline, or long-acting beta$_2$-agonist tablets.		
Step 2 Mild Persisten	One daily medication: *Anti-inflammatory: either inhaled cortico-steroid (low doses) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil). *Sustained-release theophylline to serum concentration of 5-15 mcg. / ml. is an alter-native, but not preferred therapy. Zafirlukast or zileuton may also be considered for patients 12 years of age, although their position in therapy is not fully established.	*Short-acting bronchodilator: inhaled beta$_2$-agonists as needed for symptoms. *Intensity of treatment will depend on severity of exacerbation. *Use of short-acting inhaled beta$_2$-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.	Step1 actions plus *Teach self-monitoring. *Refer to group education if available. *Review and update self-management plan
STEP 1 Mild Intermittent	*No daily medication needed.	*Short-acting bronchodilator: Inhaled beta$_2$-agonists as needed for symptoms. *Intensity of treatment will depend on severity of	*Teach basic facts about asthma. *Teach inhaler/ spacer/holding

		exacerbations. Use of short-acting inhaled beta -agonists more than 2 times a week may indicate the need to initiate long-term-control therapy.	chamber technique. *Discuss roles of medications. *Develop self-management plan *Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations. Discuss appropriate environment control measures to avoid exposure to known allergens and irritants.

From the Guidelines for the Diagnosis and Management of Asthma (1997)

The Expert Panel recommends that a detailed written action plan be developed for those patients with intermittent asthma who have a history of severe exacerbations. Intermittent asthma-infrequent exacerbations separated by periods of no symptoms and normal pulmonary function- is often mild. However, some patients with intermittent asthma experience sudden, severe and life-threatening exacerbations.

It is essential to treat these exacerbations accordingly. The patient's action plan should include indications of worsening asthma (specific symptoms and PEF measurements), as well as specific recommendations for using beta -agonist rescue therapy, early administration of systemic corticosteroids, and seeking medical care. Furthermore, periodic monitoring of the

patient is appropriate to evaluate whether the patient's asthma is indeed intermittent or whether a step-up in long-term therapy is warranted.

Persistent asthma

The Expert Panel recommends that patients with persistent asthma, either mild, moderate, or severe, receive daily long-term-control medication. The most effective long-term-control medications are those with anti-inflammatory effects, that is, those that diminish chronic airway inflammation and airway hyperresponsiveness. Evidence from clinical trials supports this recommendation (van Essen-Zandvliet et al., 1992; Kerstjens et al., 1992).

STEP 2: Mild persistent asthma. The main characteristics of step 2 care are as follows:

* Step 2 care long-term-control-medication is daily anti-inflammatory medication: either inhaled corticosteroids at a low dose, cromolyn, or nedocromil. For children, a trial of cromolyn or nedocromil is often the initial long-term therapy due to the safety profiles of these medications.

* Sustained-release theophyllin is an alternative, but preferred, long-term-control medication. It is not preferred because its modest clinical effectiveness (theophylline is primarily a bronchodilator and its anti-inflammatory activity demonstrated thus far is modest) must be balanced against concerns about potential toxicity. Theophylline remains a therapeutic option for certain patients due to expense or need for tablet-form medication.

* Sustained-release theophylline is given to achieve a serum concentration of between 5 and 15 mcg./ml.. Periodic theophylline monitoring is necessary to maintain a therapeutic - but not toxic–level.

* Zafirlukast or zileuton may also be considered an alternative long-term-control medication for patients 12 years of age and older, although their position in therapy is not yet fully established. Initial experience in clinical trials and possible patient requirements for tablet-form medication make these new medications a therapeutic option. Further clinical experience and additional data are needed to establish the role of zafirlukast and zileuton in stepwise therapy.

* Quick-relief medication must be available. Inhaled short-acting beta $_2$-agonists should be taken as needed to relieve symptoms. The intensity of treatment will depend on the severity of the exacerbation. Use of inhaled short-acting beta $_2$-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.

STEP 3: Moderate persistent asthma. Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk/ benefit outcomes. There are at least three options for initiating step 3 therapy.

* Increase inhaled corticosteroids to medium dose. This strategy will benefit many patients. Adverse effects, although infrequent, may arise.

OR

* Add a long-acting bronchodilator to a low-to-medium dose of inhaled corticosteroids. The long-acting bronchodilator may be either a long-acting inhaled beta $_2$-agonist (e.g., salmeterol) (Woolcock et al., 1996) or sustained-release theophylline (Nassif

et al., 1981); although not preferred, long-acting beta $_2$-agonist tablets may be considered. This approach has been shown to improve symptom control and may be especially beneficial in patients who have significant nocturnal symptoms. Improved asthma control has been demonstrated with an inhaled long-acting beta $_2$-agonist and a medium-dose inhaled corticosteroid compared to a doubled dose of inhaled corticosteroid (Woolcock et al., 1996), but the potential for incorrectly using long-acting inhaled beta $_2$-agonists as a quick-relief medication needs to be considered. The approach of adding theophylline has the potential for adverse reactions related to fluctuations in theophylline serum concentrations.

OR

Establish control with medium-dose inhaled corticosteroids, then lower the dose (but still within the medium-dose range) and add nedocromil. Nedocromil has a notable safety profile, and some studies (Lal et al. 1993; O'Hickey and Rees; 1994) have shown that it has some, albeit modest, inhaled corticosteroid-sparing effects in adults. Other studies (e.g., Wong et al., 1993) did not demonstrate this. Therefore, this treatment option is not preferred. Furthermore, adding another inhaler into the patient's medication schedule may affect patient adherence. It will also affect the total cost of care.

If the patient's asthma is not optimally controlled with initial step 3 therapy, and medications are used correctly, additional step 3 is recommended.

• Increase daily long-term-control medications to a high dose of inhaled corticosteroids,

AND

• Add a long-acting bronchodilator, especially to control nocturnal symptoms. The long-acting bronchodilator can be either long-acting inhaled beta $_2$ -agonist or sustained release

theophylline. An evening dose of either bronchodilator may alleviate and prevent nocturnal symptoms and thus improve adherence to the overall therapeutic regimen.

STEP 4: Severe persistent asthma. Patients whose asthma is not controlled on high doses of inhaled corticosteroids and the addition of long-acting bronchodilators will also need oral systemic corticosteroids on a regularly scheduled, long-term basis. For patients who require long-term systemic corticosteroids:

* Use the lowest possible dose (single dose daily or on alternate days).
* Monitor patients closely for corticosteroid adverse effects.

When control of asthma is achieved, make persistent attempts to reduce systemic corticosteroids. High doses of inhaled corticosteroids are preferable to systemic corticosteroids because inhaled corticosteroids have fewer systemic effects.

* Consultation with an asthma specialist is recommended.

Special considerations for managing asthma in different age groups

Infants and young children
(5 years of age and younger)
Diagnosis:

Several studies show that as many as 50 to 80% of children with asthma develop symptoms before their fifth birthday. Diagnosis can be difficult in this age group and has important implications. On the one hand, asthma in early childhood is frequently underdiagnosed (receiving such labels as chronic bronchitis, wheezy bronchitis, recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract

infections) and thus many infants and young children do not adequate therapy. On the other hand, not all wheeze and cough are caused by asthma, and caution is needed to avoid giving infants and young children inappropriately prolonged asthma therapy. Episodic or chronic wheeze, cough and breathlessness also may be seen in either less common conditions, including cystic fibrosis, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease and foreign body aspiration.

Among children 5 years of age and younger, the most common cause of asthma symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. There appear to be two general patterns of illness in infants and children who have wheezing with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood. There are no clear markers to predict the prognosis for an indivudual child; however, the factors more strongly associated with continuing asthma are allergy, a family history of allergy or asthma, and perinatal exposure to passive smoke and aeroallergens (Pullan et al., 1982; Martinez, 1995).

Diagnosis is complicated by the difficulty in obtaining objective measurements of lung function in this age group. Essential elements in the evaluation include the history symptoms, physical examination, and assessment of quality of life. A therapeutic trial with medications will also aid in the diagnosis.

Treatment:

Table (5) illustrates the Expert Panel's recommendations for a stepwise approach to managing acute and chronic asthma

symptoms, regardless of the prognosis for the wheezing infant or young child.

It is the opinion of the Expert Panel that, in general, infants and young children consistently requiring symptomatic treatment more than two times per week should be given daily anti-inflammatory medication.

At present there are few studies of medications in children younger than 3 years of age.

A therapeutic trial of anti-inflammatory medications should be monitored carefully.

Treatment should be stopped if a clear beneficial effect is not obvious. Although only inhaled corticosteroids have been shown to be effective in long-term clinical studies with infants (Bisgaard et al., 1990; Ilangovan et al., 1993), cromolyn has demonstrated symptom control and reduced airway hyperresponsiveness in a number of pediatric studies (e.g., Bertelsen et al., 1986; Hilman et al., 1987). Sustained-release theophylline, an alternative long-term-control-medication for older children, may have particular risks of adverse side effects in infants, who frequently have febrile illnesses which increase theophylline concentrations. Theophylline should be considered only if serum concentration levels will be carefully monitored.

In deciding when to initiate daily long-term-control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma vs. the possible adverse effects of medications given over prolonged periods. A preliminary study suggests that appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft, Pedersen, 1994). There is evidence that anti-inflammatory treatment can reduce morbidity from wheezing in early childhood (Connett et al., 1993). Studies in older children

suggest that the potential but small risk of delayed growth from the use of inhaled corticosteroids is balanced by their efficacy. Furthermore, there are options (cromolyn and nedocromil) for initiating anti-inflammatory therapy.

Recommendations for treating infants and young children at different steps of care include:

* The patient's response to therapy should be monitored carefully. When benefits are sustained, a step down in therapy should be attempted. If there are no clear benefits, treatment should be stopped and alternative therapies or diagnoses should be considered.

* Daily long-term-control therapy often begins with cromolyn or nedocromil.

* When inhaled corticosteroids are introduced in step 2 care, doses may range from 100 to 400 mcg./day; this generally translates to a dose of 15 mcg./day beclomethasone (Allen, Lemanske, 1993).

* When step 3 care is required, it is the opinion of the Expert Panel that control should be established promptly with higher doses of inhaled corticosteroid and then therapy should be stepped down after 2 to 3 months to maintain control (Pedersen, Hansen, 1995). For some patients, control of asthma may be maintained by using a lower dose of inhaled corticosteroid (e.g., the minimum dose in the medium-dose range) along with the addition of either nedocromil or theophylline. Some, but not all, studies with nedocromil in adults have demonstrated its potential corticosteroid-sparing effect. There are no studies demonstrating this effect with cromolyn. Studies in infants and young children are necessary. Some clinicians prefer gradually increasing medication to establish control – for example, adding nedocromil

or theophylline before increasing the dose of inhaled corticosteroid beyond low-dose therapy.

* Exacerbations caused by viral respiratory infections may be intermittent yet severe. Consider systemic corticosteroids if the exacerbation is moderate to severe or at the onset of a viral respiratory infection if the patient has a history of severe exacerbations.

* Consultation with an asthma specialist should be considered for infants and young children requiring step 2 care; consultation is recommended for those requiring step 3 or step 4 care.

* Several delivery devices are available for infants and young children. The dose received may vary considerably among devices and age groups. The child's caregivers must be instructed in the proper use of appropriately sized face masks, spacers/holding chambers with face masks and spacers/holding chambers for medication delivery to be effective and efficient. For children younger than 2 years of age, nebulizer therapy may be preferred for administering cromolyn and high doses of beta$_2$-agonists during exacerbations. Children between 3 and 5 years may begin therapy with MDI and spacer/holding chamber alone, but if the desired therapeutic effects are not achieved, they may require a nebulizer or an MDI plus spacer/holding chamber and face mask.

School-age children
(Older than 5 years of age and adolescents)

The pharmacologic management of school-age children and adolescents follows the same basic principles as those for adults, but the special circumstances of growth, school and social development require special consideration.

Assessment:

Pulmonary function testing should be performed using comparison data from an appropriate reference population (American Thoracic Society 1991). Adolescents generally compare better to childhood than to adult predicted norms. Testing in a laboratory or clinic specializing in children can result in higher pulmonary function values and more consistent data. Technicians who conduct pulmonary function testing for children should have special training in achieving the best possible effort from young patients.

Treatment:

For children with mild or moderate persistent asthma, cromolyn or nedocromil are often effective anti-inflammatory therapies and have no known long-term systemic effects. However, for children with severe persistent asthma, and for many children with moderate persistent asthma, cromolyn and nedocromil do not provide adequate control and thus inhaled corticosteroids are necessary for long-term therapy.

The Expert Panel recommends that adolescents (and younger children as appropriate) be directly involved in developing their asthma management plans. Adolescents may experience more difficulties than younger children in adhering to a medication plan because they may fail to recognize the danger of poorly controlled asthma (Strunk et al., 1985), they may not accept having a chronic illness, or they may view the plan as infringing upon their emerging independence and adulthood. In treating adolescents the same asthma self-management techniques expected of adults, the clinician should address adolescent developmental issues such as building a positive self-image and confidence, increasing personal responsibility and gaining problem-solving skills. To accomplish this, it is often helpful to see the adolescent initially without parents present and to involve the adolescent directly in setting goals for therapy,

developing an appropriate treatment plan, and reviewing the effectiveness of the plan at repeated visits. The parents can be brought in at the end of the visit to review the plan together and emphasize the parents' important role in supporting the adolescent's efforts.

Table 5: Stepwise approach for managing infants and young children (5 years of age and younger) with acute or chronic asthma symptoms.

	Long-term control	Quick relief
STEP 4 Severe persistent	*Daily anti-inflammatory medicine - High-dose inhaled corticosteroid with spacer/holding chamber and face mask If needed, add systemic corticosteroids 2 mg./kg./day and reduce to lowest daily alternate-day dose that stabilizes symptoms.	*Bronchodilator as needed for symptoms up to 3 times a day.
STEP 3 Moderate persistent	*Daily anti-inflammatory medication. Either: - Medium-dose inhaled corticosteroid wi spacer/holding chamber and face mask OR, once control is established: Medium-dose inhaled corticosteroid and nedocromil OR Medium-dose inhaled corticosteroid and Long-acting bronchodilator (theophylline).	*Bronchodilator as needed for symptoms up to 3 times a day.
STEP 2 Mild persistent	*Daily anti-inflammatory medication. Either - Cromolyn (nebulizer is preferred; or MDI) or nedocromil (MDI only). Infants and young children usually begin with a trial of cromolyn or nedocromil OR low-dose inhaled corticosteroid with spacer/holding chamber and face mask.	*Bronchodilator as neededfor symptoms.
STEP 1 Mild intermittent	*No daily medication needed.	* Bronchodilator as needed for symptoms <2 times a week. Intensity of treatment will depend upon severity of exacerba-

		tion. Either: Inhaled short-acting beta $_2$-agonist by nebulizer or inhaler with a spacer/holding chamber OR Oral beta$_2$-agonist for symptoms. With viral respiratory Infection Bronchodilators every 4-6 hours up to 24 hours but repeat no more than once every 6 weeks. Consider systemic corticosteroid if: Current exacerbation is severe OR Patient has history of previous severe exacerbations.
Step down Review treatment every 1 to 6 months. Control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.		Step up If control is not achieved, consider step up. but first: review patient medication technique, adherence and environmental control (avoidance of allergens or other precipitant factors).

From Guidelines for the Diagnosis and Management of Asthma (1997).

School issues:

The clinician should prepare a written asthma management plan for the student's school that includes the following information: an action plan for handling exacerbations (including the clinician's recommendation regarding self-administration of medication and plans to ensure prompt, reliable access to medications); recommendations for long-term-control medica-

tions and prevention of exercise-induced bronchospasm (EIB), if appropriate; and identification of those factors that make the student's asthma worse so the school may help the student avoid exposure.

It is preferable to schedule daily, long-term medications so that they are not taken at school, even if this results in unequal dosing intervals throughout the day. However, in school districts that have more comprehensive school nurse coverage, children who would benefit from close supervision to promote adherence may be given medications at school. In this way, daily medication can be administered and patient education can be supplemented most days of the week.

Students with asthma often require medication during school to treat acute symptoms or to prevent EIB that may develop during physical education class, school recess, or organized sports. Reliable, prompt access to medication is essential, but it may be difficult because of school rules that preclude the child from carrying medications. The National Asthma Education and Prevention Program and several member organizations have adopted resolutions that endorse allowing students to carry and self-administer medications when the physician and parent consider this appropriate. It may be helpful for some children to have a compressor-driven nebulizer available at the school.

Sports:

Physical activity at play or in organized sports is an essential part of a child's life, and full participation in physical activities should be encouraged. Many children with asthma experience cough, wheeze, or excessive fatigue when they exercise.

Treatment immediately prior to vigorous activity or exercise usually prevents EIB. If symptoms occur during usual play activities, a step up in long-term therapy is warranted.

Poor endurance or EIB can be an indication of poorly controlled persistent asthma; appropriate use of long-term-control medication can reduce EIB. Activity should be limited or curtailed only as a last resort.

Older adults

Because of the high prevalence of other obstructive lung disease (e.g., chronic bronchitis, emphysema) among the elderly, it is important to determine the extent of reversible airflow obstruction. Careful evaluation is required because the precise cause of severe airflow obstruction can be difficult to identify in older patients with asthma. A 2- to 3-week trial of therapy with systemic corticosteroids can help detect the presence of significant reversibility of the airway disease. Long-term-control asthma medication can then be offered.

Asthma medications may have increased adverse effects in the elderly patient; adjustments in the medication plan may be necessary.

Airway response to bronchodilators may change with age, although this is not clearly established. Older patients, especially those with preexisting ischemic heart disease, may also be more sensitive to beta ₂-agonist side effects, including tremor and tachycardia. Concomittant use of anticholinergics and beta ₂-agonists may be beneficial to the older patients (Gross et al., 1989; Barros, Rees, 1990).

Theophylline clearance is reduced in the elderly patient (Nielsen-Kudsk et al., 1988), causing increased blood levels of theophylline. In addition, age is an independent risk factor for developing life-threatening events from iatrogenic chronic theophylline overdose (patients 75 years of age or older have a

16-fold greater risk of death from theophylline overdose than do 25-year-olds) (Shannon, Lovejoy, 1990). The potential for drug interaction –especially with antibiotics and H_2 -histamine antagonists such as cimetidine- is greater because of the increased use of medications in this age group. Theophylline and epinephrine may exacerbate underlying heart conditions. Systemic corticosteroids can provoke confusion, agitation and changes in glucose metabolism.
A dose-dependent reduction in bone mineral content may be associated with inhaled corticosteroid use, although low or medium doses appear to have no major adverse effect. Elderly patients may be more at risk due to preexisting osteoporosis, changes in estrogen levels that affect calcium utilization, and a sedentary lifestyle. However, the risk of not adequately controlling asthma may unnecessarily limit the patient's mobility and activities. Concurrent treatment with calcium supplements and vitamin D, and estrogen replacement when appropriate, are recommended. At the present time, the optimal approach for identifying patients at risk for accelerated bone loss from high-dose corticosteroid therapy is to conduct bone densitometry when treatment begins and again 6 months later (NHLBI, 1996), although the benefits of this approach have not yet been evaluated in clinical trials.

Medications employed for other diseases may exacerbate asthma; adjustments may need to be made. Nonsteroidal anti-inflammatory agents for treating arthritis, nonselective beta-blockers for treating hypertension, or beta-blockers found in some eye drops used to treat glaucoma may exacerbate asthma.

Managing special situations in asthma

Seasonal asthma

Some patients experience asthma symptoms only in relationship to certain pollens and molds. Such seasonal asthma should be treated according to the stepwise approach to long-term management of asthma. If the patient has seasonal asthma on a predictable basis, daily, long-term anti-inflammatory therapy (inhaled corticosteroids, cromolyn, or nedocromil) should be initiated prior to the anticipated onset of symptoms and continued through the season.

Cough variant asthma

Cough variant asthma is seen especially in young children. Cough is the principal symptom; because this frequently occurs at night, examinations during the day may be normal. Monitoring of morning and afternoon PEF variability and/or therapeutic trials with anti-inflammatory or bronchodilator medication may be helpful in diagnosis. Once the diagnosis is established treat according to the stepwise approach to long-term management of asthma.

Exercise-induced bronchospasm

Exercise-induced bronchospasm- which if untreated can limit and disrupt otherwise normal lives- should be anticipated in all asthma patients. EIB is a bronchospastic event that is caused by a loss of heat, water, or both from the lung during exercise because of hyperventilation of air that is cooler and dryer than that of the respiratory tree (Godfrey, 1986; McFadden, Gilbert, 1994). EIB usually occurs during or minutes after vigorous activity, reaches its peak 5 to 10 minutes after stopping the activity and usually resolves in another 20 to 30 minutes.

Exercise may be the only precipitant of asthma symptoms for some patients. These patients should be monitored regularly to ensure that they have no symptoms of asthma or reductions in

PEF in the absence of exercise, because EIB is often a marker of inadequate asthma management and responds well to regular anti-inflammatory therapy.

Diagnosis:

A history of cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during exercise suggests EIB. An exercise challenge can be used to establish the diagnosis. This can be performed in a formal laboratory setting or as a free-run challenge sufficiently strenuous to increase the baseline heart rate to 80% of maximum for 4 to 6 minutes. Alternatively, the patient may simply undertake the task that previously caused the symptoms. A 15% decrease in PEF or FEV_1 (measurement taken before and after exercise at 5-minute intervals for 20 to 30 minutes) is compatible with EIB.

Management strategies:

One goal of management is to enable patients to participate on any activity they choose without experiencing asthma symptoms. EIB should not limit either participation or success in vigorous activities.

Recommended treatments include:

* Beta $_2$-agonists will prevent EIB in more than 80% of patients.
* Short-acting inhaled beta $_2$-agonists used shortly before exercise (or as close to exercise as possible) may be helpful for 2 to 3 hours.
* Salmeterol has been shown to prevent EIB for 10 to 12 hours (Kemp et al., 1994)
* Cromolyn sodium and nedocromil, taken shortly before exercise, are also acceptable for preventing EIB (de Benedictis et al., 1995).
* A lengthy warmup period before exercise may benefit patients who can tolerate continuous exercise with minimal

symptoms. The warmup may preclude a need for repeated medications.

* Long-term-control therapy, if appropriate. There is evidence that appropriate long-term control of asthma with anti-inflammatory medication will reduce airway responsiveness, and this is associated with a reduction in the frequency and severity of EIB (Vathenen et al., 1991).

Teachers and coaches need to be notified that a child has EIB, should be able to participate in activities and may need inhaled medication before activity. Individuals involved in competitive athletics need to be aware that their medication use should be disclosed and should adhere to standards set by the Olympic Committee (Nastasi et Al., 1995).

Surgery and Asthma

Asthma patients are at risk for specific complications during and after surgery: acute bronchoconstriction triggered by intubation, hypoxemia and possible hypercapnia, impaired effectiveness of cough, atelectasis and respiratory infection (Kingston, Hirshman, 1984) and latex exposure (Sussman, Beezhold, 1995). The likelihood of these complications depends on the severity of the patient's airway hyper-responsiveness, airflow obstruction, mucus hypersecretion and latex sensitivity. Recommended actions include:

* Patients with asthma should have an evaluation before surgery that includes a review of symptoms, medication use (particularly the use of systemic corticosteroids for longer than 2 weeks in the past 6 months) and measurement of pulmonary function.

* If possible, attempts should be made to improve lung function (FEV_1 or PEF) to their predicted values or their

personal best level. A short course of systemic corticosteroids may be necessary to optimize pulmonary function.

* For patients who have received systemic corticosteroids during the past 6 months, give 100 mg. hydrocortisone every 8 hours intravenously during the surgical period and reduce dose rapidly within 24 hours following surgery.

Pregnancy and asthma

Maintaining sufficient lung function and blood oxygenation to ensure adequate oxygen supply to the fetus is essential. Poorly controlled asthma during pregnancy can result in increased perinatal mortality, increased prematurity, and low birth weight (Nelson, Weber, 1988). For most drugs used to treat asthma and rhinitis, with the exception of brompheniramine, epinephrine and alpha-adrenergic compounds (other than pseudoephedrine), there is little to suggest an increased risk to the fetus (Schatz et al., 1988). Other classes of drugs with some possibility of risk to the fetus include decongestants (other than pseudoephedrine), antibiotics (tetracycline, sulphonamides and ciprofloxacin), live virus vaccines, immunotherapy (if doses are increased) and iodides.

Stress and asthma

The role of stress and psychological factors in asthma is important but not fully defined. There is emerging evidence that stress can play an important role in precipitating exacerbations of asthma and possibly act as a risk factor for an increase in prevalence of asthma (Busse et al., 1995). The mechanisms involved in this process have yet to be fully established and may involve enhanced generation of proinflammatory cytokines (Friedman et al., 1994). Equally important are psychosocial factors that are associated with poor outcome (e.g., conflict

between patients and family and the medical staff, inappropriate asthma self-care, depressive symptoms, behavioral problems, emotional problems and disregard of perceived asthma symptoms (Strunk et al., 1993; Brush, Mathe, 1993).

SINUSITIS

In general terms, sinusitis can be defined as inflammation of the paranasal sinuses (Malow, Creticos, 1989), the etiology of which includes both infectious agents and allergic mechanisms. The most significant risk factor for the development of sinusitis is a prior viral upper respiratory tract infection (URI); it is estimated that 0.5% of cases of URI are complicated by sinusitis (Bamberger, 1991). The reason that the exact incidence is difficult to determine is that clinically the early symptoms of sinusitis are indistinguishable from a simple URI. However, recent advances in radiologic imaging and new endoscopic techniques have improved both diagnostic and therapeutic capabilities. While sinusitis can be categorized in many ways, the most common description is by the duration of symptoms. Therefore, acute sinusitis refer to symptoms lasting less than 4 weeks; subacute sinusitis 4 weeks to 3 months; and chronic sinusitis longer than 3 months (Wald, 1989; Stafford, 1990).

Pathogenesis:

Bacterial sinusitis:

The pathogenesis of sinusitis is multifactorial and involves a complex interaction between host defense mechanisms and the infecting organism. In order to understand the pathologic events that result in clinical sinusitis, it is necessary to review the normal physiology of the paranasal sinuses.

The key to normal sinus function is the mucociliary transport system. The nose and paranasal sinuses are lined by ciliated pseudostratified columnar epithelium (Yonkers, 1992). Epithelial goblet cells and submucosal seromucous glands produce a secretory blanket that has two components – a surface mucous layer and a deeper aqueous layer (Wagenmann, 1992; Kaliner, 1992). Ciliary action moves the mucus layer toward the natural sinus ostia and then to the nasopharynx. Replenishment of the mucous layer is an ongoing process. Mucociliary transport functions as a barrier to infection by removing bacteria and inhaled particulate matter from the nose and sinuses. Moreover, the aqueous layer beneath the mucus contains immunoglobulins such as secretory IgA, IgG, IgM, and other molecules that contribute to host defense (Kaliner, 1992). Alteration in sinus ostia patency, ciliary function, or quality of secretions causes disruption of the system and leads to sinusitis (Wald, 1992).

The most important factor in the pathogenesis of sinusitis is the patency of the sinus ostia (Slavin, 1988). The normal size of the ostium varies for the different sinuses but may be as small as 1 to 2 mm, which is the usual diameter of the ostia of the ethmoid sinus. Ostium size may decrease further under normal activities such as recumbency and perhaps during nasal cycle because of mucosal congestion (Malow, 1989). It is generally felt that the most common cause of sinus ostial obstruction, and thus secondary acute sinusitis, is viral upper respiratory tract infection (Gwaltney, 1979; Turner et al., 1992) with more than half of individuals with viral upper respiratory tract infections demonstrating thickening of the sinus mucosa on radiographic imaging (Rachelefsky et al., 1984; Naclerio, 1991; Slavin, 1991). Because of their unique anatomic structure with narrow ostia, the ethmoid sinuses are probably the most susceptible to ostial

obstruction and infection. While usually the whole complex is affected, occasionally just a group of cells will be diseased. While obstruction of the sinus ostia in acute sinusitis is most often due to mucosal edema, in chronic sinusitis, an anatomic abnormality that interferes with drainage through the ostia is frequently present.

Obstruction of the sinus ostia, partial or complete, results in stagnation of secretions, decreased pH (Reilly, 1990) and lowered oxygen tension within the sinus (Carenfelt et al., 1977; Drettner et al., 1977). These changes create an environment that favors bacterial growth (Reilly, 1990). Stagnant secretions and bacterial infection in turn cause mucosal inflammation. Subsequent damage to the mucosal epithelium and the cilia is, in large part, due to proteolytic enzymes released by leukocytes. True bacterial mucosal invasion is uncommon. With the additional swelling of the mucosa, the sinus ostia obstruct completely and the "sinusitis cycle" described by Reilly (Reilly, 1990) is perpetuated. Oxygen tension within an obstructed sinus may drop to virtually zero, promoting growth of anaerobic and facultative bacteria (Carenfelt et al., 1977; Drettner et al., 1977), which has important implications in chronic sinusitis. Host defense mechanisms are impaired by conditions of low oxygen tension with the generation of oxygen free radicals by leukocytes being depressed, which impairs bacterial killing (Malow et al., 1989). Leukocyte function is further impaired by the low concentration of IgA, IgG, and IgM found in purulent sinus secretions (Daley et al., 1988).

Disruption of mucociliary transport in the paranasal sinuses is another key in the pathogenesis of sinusitis. Normal ciliary beat frequency is greater than 700 beats per minute; however, during sinusitis, the ciliary beat frequency decreases to less than 300

beats per minute. In addition, the inflammation stimulates the conversion of ciliated cells to mucus-secreting goblet cells and eventually irreversible change of the respiratory epithelium occurs (Yonkers, 1992).

In addition, the quality and character of sinus secretions change during sinusitis. Inspissated mucus, which cannot be cleared effectively from the sinuses, becomes a source of inflammation and a culture medium for bacterial growth. In addition, thickened secretions block the sinus ostia and stimulate the sinusitis cycle. This is a particular problem in patients with cystic fibrosis with failure of exocrine gland function, which results in thickened sinus secretions with the majority of patients developing sinusitis (Ramsey et al., 1992).

Of note is the relatively recent discovery that normal paranasal sinuses are not sterile and, in fact, harbor the same bacteria that cause acute sinusitis, confirming the important role of obstruction of the ostia. Brook demonstrated that 12 out of 12 normal patients grew anaerobic organisms, from their maxillary sinuses, with seven also growing aerobic organisms (Brook, 1971). The anaerobes isolated in this study were predominantly Bacteroides species, anaerobic gram-positive cocci, and Fusobacterium. Predominant aerobes were β- and α-hemolytic Streptococci, Streptococcus pneumoniae, Hemophilus influenzae, and Staphylococcus aureus. Likewise, Su and colleagues (Su et al., 1983) found aerobic and facultative bacteria in the sinuses of seven normal patients.

Fungal sinusitis:

Fungal infection of the sinuses involves a spectrum of disease ranging from a fungus ball in the sinus to invasive fungal sinusitis. Fungal sinusitis most commonly afflicts

immunosupressed patients or those with chronic debilitating diseases such as diabetes mellitus.

Fungal sinusitis can be categorized into noninvasive, invasive, and allergic fungal sinusitis.

Noninvasive fungal sinusitis occurs in immunocompetent hosts as a localized process. It usually involves the maxillary sinus and runs an indolent course. Occasionally, it may occur in an apparently normal host. Sinus ostial obstruction is the most likely precipitating event in this type of sinusitis as hypoxic conditions favor fungal growth (Parnes et al., 1989). Inoculation of the sinus with a massive fungal load is another possible pathogenic mechanism (Corey et al., 1990). The nidus of fungal infection slowly increases in size within the sinus (fungus bolus without true invasion of tissue, although erosion of bone due to pressure is possible, but most unusual). Invasive fungal sinusitis occurs predominantly as an opportunistic infection in an immunocompromised host. Patients with lymphoproliferative neoplasms such as acute leukemia are at highest risk (Kavanagh et al., 1991). In acute disease, invasion of blood vessels by fungi lead to thrombosis of the vessels and ultimately tissue necrosis. Destruction of surrounding bone is common and the risk of disseminated disease is significant.

Allergic fungal sinusitis was recognized as a separate clinical entity in 1983 by Katzenstein et al. (Katzenstein et al., 1983), he described seven cases of allergic Aspergillus sinusitis in normal hosts. Histopathologically, allergic Aspergillus sinusitis is indistinguishable from allergic bronchopulmonary aspergillosis with mucinous material containing eosinophils, Charcot-Leyden crystals, fungal hyphae found in both conditions. The pathogenesis of allergic fungal sinusitis probably involves a

combination of types I and III Gell and Coombs hypersensitivity reactions (Corey et al., 1990). Eosinophils and fungus-specific IgE play a central role in the local tissue response: Mucosal inflammation and thickened, inspissated mucus (allergic mucin) contribute to ostial obstruction and local tissue hypoxia, which promotes fungus growth (Corey, 1992). Histologically, only a small amount of fungi are detected in allergic mucin and there is evidence of tissue invasion. Bone erosion can occur in longstanding cases (Katzenstein et al., 1983).

Etiology:

Predisposing factors:

There are several well-recognized predisposing factors for bacterial sinusitis. As already stated, the most common of these is recurrent viral upper respiratory tract infections (Gwaltney, 1979). In normal hosts, a viral URTI increases the amount and decreases the viscosity of the mucus. Ciliated cells can be damaged severely by the viral infection and may take many months to recover normal function. Other predisposing factors for acute bacterial sinusitis include allergy, dental procedures, presence of a foreign body (e.g., nasotracheal tube, nasogastric tube, or nasal packing), and barotrauma. Iatrogenic causes of sinusitis are obviously becoming increasingly prevalent. Kaplan and Hoyt (Kaplan et al., 1982) studied adult patients hospitalized in a trauma unit and found that sinusitis accounted for 5% of all nosocomial infections observed over a 2-year period. Nosocomial sinusitis occurred in 100% of patients on mechanical ventilation. 81% of patients with nasogastric tubes, 34% of patients with facial or cranial fractures, 19% of patients with nasotracheal tubes, and 6% of patients with nasal packing. In a separate study of 111 head trauma patients by Grindlinger at al. (Grindlinger,

1987), sinusitis developed in 19 patients, 16 of whom had nasotracheal intubation as opposed to oral tracheal intubation.

Factors that predispose to chronic sinusitis include allergic rhinitis, aspirin sensitivity with hypertrophic rhinitis, nasal polyposis, various immunodeficiency disease syndromes, anatomical disorders such as septal deviation, cystic fibrosis, and immotile cilia syndromes.

Risk factors for fungal sinusitis are related to the patient's immune competency. While unusual in a normal host, fungal sinusitis occurs as a result of either hypersensitivity to the fungus (Katzenstein, 1983) or as a result of changes in the local tissue milieu within the sinus, which favor fungal growth (Corey, 1992). Immunocompromised hosts are at risk for opportunistic fungal infections that may be life-threatening. Diabetics who develop fulminant mucormycosis infection are an example. The most significant immune deficiencies predisposing to invasive fungal sinusitis involve T-cell deficits and severe neutropenia (Corey et al., 1990).

Bacteriology:

Acute Bacterial Sinusitis:

The bacterial pathogens responsible for acute sinusitis in adults have been identified in studies by performing maxillary sinus aspiration on previous untreated patients. These show that nonencapsulated Hemophilus influenza and Streptococcus pneumoniae account for the majority of community-acquired sinusitis (Winther et al., 1990; Gwaltney, 1992; Wald, 1998). Anaerobic organisms such as Bacteroides, Peptostreptococcus,

and Fusobacterium account for only 6% to 10% of acute sinus infections and are usually associated with dental infections (Winther, 1990). The prevalence of β-lactam-producing strains of Hemophilus influenzae and Streptococcus pneumoniae has increased in recent years. In one study, 52% of H. influenzae strains were β-lactam producers (Gwaltney, 1992).

In children, the bacteria responsible for acute sinusitis are nearly the same as that for adults, with H. influenzae and S. pneumoniae playing a major role. However, Moraxella catarrhalis is responsible for approximately 20% of acute sinusitis in children. Both H. influenzae and M. catarrhalis may be β-lactamase producing, making them resistant to amoxycillin (Wald, 1992). The prevalence of resistant strains varies with geographic location. Recently, 75% of M. catarrhalis and 30% of H. influenzae were found to be β - lactam positive in the Pittsburgh area (Wald, 1992).

In nosocomial sinusitis, gram-negative bacteria predominate. In Kaplan and Hoyt's study (Kaplan, 1982), Pseudomonas aeroginosa was the most common organism isolated, followed by Klebsiella pneumoniae, Entero-bacter species, Proteus mirabilis, and Escherichia coli. In the Grindlinger et al. (1987) study of head-injured patients, the most common gram-negative bacilli were Pseudomonas aeruginosa and Escherichia coli. Occasionally, nosocomial sinusitis can be caused by Actinomyces or Nocardia.

Chronic Bacterial Sinusitis:

Anaerobes play a significant role in chronic sinusitis in adults (Su et al., 1983; Frederick et al., 1974). In a recent study, Brook (Brook, 1994) found that anaerobes were present in 51% of

culture-positive specimens from adults with chronically inflamed maxillary sinuses. Predominant anaerobes were anaerobic cocci and Bacteroides species. In 21 cases (31% of aspirates), a mixture of aerobes and anaerobes was isolated. Streptococcus species and Staphylococcus aureus were the predominant aerobes. Brook (Brook, 1989) theorized that β-lactam-producing anaerobes liberate the enzyme into the sinus cavity, thereby protecting penicillin-susceptible bacteria, which may account for the presence of a mixed flora.

The microbiology of chronic sinusitis in children is more controversial than in adults in terms of the prevalence of anaerobic organisms. Brook (Brook, 1981) isolated anaerobes such as anaerobic cocci, Bacteroides, or Fusobacterium in 37 out of 40 patients with chronic sinusitis. Staphylococcus aureus was the most common aerobic organism found. Muntz and Lusk (Muntz et al., 1991) however, isolated anaerobes in only 6% of cases of children with chronic sinusitis. Review of the methodology and patient population in these studies has led Wald (Wald, 1992) to conclude that in children with longstanding symptoms or symptoms severe enough to require surgery, anaerobic organisms and Staphylococci should be suspected.

Fungal Sinusitis:

Noninvasive fungal sinusitis is most commonly caused by Aspergillus species (Corey et al., 1990), but other organisms have been reported including Pseudallescheria boydii, Schizophyllum commune and Alternaria species (Bamberger, 1991). Aspergillus species is also the most common organism responsible for invasive fungal sinusitis in immunocompromised patients. In a recent study, Candida was a distant second to

Aspergillus as an etiologic agent in sinusitis afflicting immunocompromised children (Kavanagh et al., 1991). Mucor species and Pseudallescheria boydii have also been reported (Bamberger, 1991). While Aspergillus was the initial pathogen identified in allergic fungal sinusitis, many other fungal species have been implicated. Bipolaris specifera (Gourley, 1990), Alternaria species, and Curvularia lunata have all been implicated in allergic fungal sinusitis (Corey, 1992).

Clinical evaluation:

In general, sinusitis complicating a viral upper respiratory tract infection diffusely involves all the paranasal sinuses to some degree (pansinusitis). If the acute infection involves one sinus, an underlying cause should be sought (e.g., dental infection or local anatomic abnormality).

Bacterial sinusitis:

The clinical features of acute bacterial sinusitis in adults are difficult to distinguish from the common cold or even allergic rhinitis in the early phase of illness. Purulent nasal discharge and facial pain are the most common clinical findings in acute sinus infection (Malow et al., 1989; Evans, 1998). The location of the facial pain is related to the particular sinus involved. Typically, the maxillary sinusitis causes pain in the cheek while ethmoid sinusitis is felt most in the area of the medial canthus. Frontal sinusitis typically gives pain in the region of the forehead and medial orbit, while sphenoid sinusitis produces retro-orbital or occipital pain. Other less frequent signs and symptoms include vague headache, halitosis, anosmia, and post-nasal drip with cough. Fever is present in 50% of adult patients with acute sinusitis (Stafford, 1990).

Physical examination often reveals a mucopurulent discharge in the region of the middle meatus, which can be secondary to maxillary, ethmoid, or frontal sinusitis. Pus in the region of the superior meatus implicates the posterior ethmoid or sphenoid sinuses. In addition, the mucosa is diffusely congested. The paranasal sinuses may be tender to palpation. In the case of dental infection secondarily involving the maxillary sinus, the offending tooth is usually tender to percussion.

The symptoms of chronic bacterial sinusitis in adults are similar to those of acute sinusitis except that the nasal congestion and purulent nasal discharge are protracted (Malow, 1989). Evidence of purulence emanating from the sinuses is usually present on physical examination and the underlying cause for chronicity is usually apparent as for example, an anatomic obstruction of the sinus ostium is often found. Nasal polyps, deviated nasal septum and persistent mucosal edema from recurrent infection or allergy are just a few of the possible etiologic causes of chronicity.

The symptoms of acute bacterial sinusitis in children are less specific than in adults (Daele, 1997). Children are less likely to complain of headache and facial pain. Rather, symptoms of a URI such as nasal congestion and day dry cough that persist beyond 7 days are suspicious of sinusitis (Wald, 1992). In addition, children with a high fever (greater than 39°C) and purulent nasal discharge associated with an upper respiratory infection probably have sinusitis, especially if there is associated mild periorbital edema (Fireman, 1992). Physical examination is less informative in children than in adults in terms of the diagnosis of sinusitis. One may detect mild facial swelling over the involved sinus or occasionally periorbital swelling. Tenderness over the maxillary sinus is often present (Fireman,

1992). Intranasal examination is limited to anterior rhinoscopy except in older children. Evidence of pus in the nose and the presence of a deviated nasal septum can often be detected by this method. Flexible or rigid endoscopy improves visualization of the sinuses drainage areas and can be used on occasion in the children (Lusk et al., 1989).

Subacute and chronic sinusitis in the pediatric age group usually manifests as purulent rhinorrhea with or without postnasal drip.

Cough and occasionally episodes of wheezing can be present as well (Tinkelman, 1989). Often about 50% of children with chronic sinusitis demonstrate associated chronic otitis or recurrent otitis media, also chronic sinusitis is frequently diagnosed in children with asthma or allergic rhinitis (Fireman, 1992). As in adults the child suspected of having chronic sinusitis must be evaluated for a mechanical obstruction of the sinus ostia.

Fungal sinusitis:

Noninvasive fungal sinusitis is an indolent disease process that usually affects only one sinus. Characteristic symptoms include nasal congestion and facial pain (Malow et al., 1989), but it may be asymptomatic.

Symptomatologic findings on physical examination usually do not distinguish this condition from chronic bacterial infection. It can, however, present with a mass effect, distorting the orbit and for practical purposes resembling a neoplasm.

Patients with allergic fungal sinusitis are typically healthy young adults with nasal polyposis, a history of asthma, and

chronic sinusitis, and chronic sinusitis refractory to medical therapy. In addition, many patients have had some form of sinus surgery without relief of symptoms. It is difficult to distinguish allergic fungal sinusitis from chronic bacterial sinusitis on clinical grounds. For this reason, immunologic parameters (eosinophil count, antigen-specific IgE levels, skin sensitivity tests) and radiologic criteria are helpful to make the diagnosis preoperatively (Corey, 1992).

Invasive fungal sinusitis is a fulminant disease that occurs most often in immunocompromised patients. Facial pain and fever were the most common clinical findings noted in a series of pediatric patients with neoplasms who developed invasive fungal sinusitis (Kavanagh et al., 1991). However, adults patients may be desperately ill with fungal invasion of blood vessels causing tissue ischemia and necrosis. This initially presents as black mucosal patches in the nose and palate (e.g., mucormycosis in diabetics). Progression of disease is rapid and may include intracranial extension and death (Corey et al., 1990). For this reason, a high index of suspicion should compel the clinician to constantly examine the nose for early signs of necrosis.

Special investigations:

A variety of diagnostic maneuvers and procedures are available to aid the clinician in establishing the diagnosis of sinusitis. The simplest of these maneuvers is transillumination of the maxillary and frontal sinuses, which, although still practiced by some clinicians, has been pretty much abondoned because of concern as to its clinical significance. In patients with a dull maxillary sinus on transillumination, only one-third were found to have culture-positive sinus aspirates (Winther et al., 1990), leading some authors to suggest that this technique should be

discarded (Druce, 1992). More sensitive diagnostic modalities such as the computed tomography (CT) scan and the use of fibreoptic endoscopy have also discouraged the use of transillumination. Despite these objections, transillumination is useful in following patients for resolution of an opacified maxillary sinus initially demonstrated by sinus radiography, thereby avoiding multiple radiation exposures, particularly in patients who are pregnant (Richtsmeier, 1992). Wald argues that in children over 10 years of age, transillumination of the sinuses is useful if it is interpreted as being completely normal (Wald, 1992).

Nasal culture for the purpose of identifying pathogenic organisms in sinusitis is not advised. Poor correlation between nasal culture results and sinus aspiration results has been well documented with contamination by Staphylococcus aureus being the major confounding problem (Gwaltney, 1981).

Nasal cytology has been described as a means of differentiating acute sinus infection (polymorphonuclear cells) from allergic rhinitis (eosinophils). While this method is sensitive (Wilson, 1988), it is not, in our opinion, of any real value and certainly not a substitute for sinus radiography (Gill et al., 1989).

Nasal endoscopy using the newer rigid endoscopes has greatly improved the ability to diagnose and evaluate the results of therapy for sinusitis. Visualization of the accessible components of the osteomeatal complex and a thorough evaluation of nasal anatomy are certainly possible (Kennedy, 1990) and easily performed as an office procedure under topical anesthesia. Nasal endoscopy is most suitable for adult and adolescent patients, who

can cooperate as needed, but is less suitable for young children (Fireman, 1992).

Aspiration of the maxillary sinus secretions for microscopy, culture, and sensitivity has been suggested as a diagnostic technique in those cases of sinusitis refractory to medical therapy, or in patients who are at increased risk, such as immunocompromised patients (Wald, 1992). Puncture is performed transnasally via the inferior meatus under local anesthesia. This can be performed quite easily in most adults and older children. While a complete blood count and sedimentation rate have little clinical value in the evaluation of patients with symptoms of sinusitis, an absolute eosinophil count, fungus-specific IgE levels, and immediate skin test to fungal antigens are important in the diagnostic workup for fungal sinusitis (Corey et al., 1990; Gourley et al., 1990).

Imaging

The radiologic evaluation of patients with sinusitis can involve a wide range of techniques that differ in their sensitivity, specificity, indications, costs, and risks to the patient. The four modalities in current use include sinus plain films, ultrasound, CT scan, and MRI scan.

Sinus Radiographs

Plain films of the sinus are the traditional imaging technique used in evaluating patients with symptoms of sinusitis. A routine sinus series includes anteroposterior, lateral, and occipitofrontal projections (Kovatch et al., 1984). While plain films provide a rapid and noninvasive evaluation of the maxillary, frontal,

sphenoid, and posterior ethmoid sinuses and the lower one-third of the nasal cavity, the critical area of the osteomeatal complex and the anterior ethmoid sinuses are poorly visualized (Zinreich, 1992). The specificity and sensitivity of sinus films have been examined in several studies, which compared the results of radiographs with the results of maxillary sinus puncture. From these studies, it is clear that a significant number of patients with radiographic sinus abnormalities do not have sinusitis (Kuhn, 1986). The most reliable and specific signs of sinusitis on radiographs include sinus opacification,

Mucosal thickening greater than 3 mm, and air-fluid levels. While very specific, these findings yield a sensitivity of approximately 50% (Kuhn, 1986). Problems with interpretation of plain films of the sinuses are magnified in children. In one study, 50% of children with no clinical evidence of sinusitis had opacified sinuses on radiograph (Maresh et al., 1940). In contrast, Kovatch et al. (Kovatch et al., 1984) found that in children older than 1 year without signs or symptoms of upper respiratory infection, abnormal maxillary sinus radiographs were infrequent. They questioned whether adequate screening of the control group for evidence of URI had been done in previous studies.

Despite conflicting data, several points regarding the usefulness of sinus plain films can be made. A clear sinus radiograph makes significant sinus pathology unlikely. The presence of air-fluid level in the sinus is significant in all age groups, whereas mucosal thickening remains nonspecific especially in young children. Unilateral complete opacification of a sinus is clearly abnormal and correlates well with sinusitis (Kuhn, 1986).

In summary, the usefulness of sinus radiographs in the evaluation of both children and adults with sinusitis has been diminished by the emergence of more sensitive and specific techniques such as nasal endoscopy and CT scan. However, the expense of newer modalities and the need for sedation of pediatric patients mean that sinus radiographs will likely continue to play a role in the evaluation of patients with sinusitis (Diament, 1992).

Computed tomography

Computed tomography (CT) is now recognized as the single best imaging technique for paranasal sinus disease. Optimal demonstration of the ethmoid sinuses and the osteomeatal complex is achieved with thin coronal sections. Axial sections are most helpful in the evaluation of orbital complications of sinusitis. Contrast injection is rarely necessary for a benign process but may be of value if there is concern that malignant disease may coexist with bone destruction or extension outside the sinus (Diament, 1992). CT scan of the paranasal sinuses is indicated in the evaluation of chronic refractory sinusitis, sinusitis with complications, or possible underlying malignancy. It is also used for preoperative evaluation before endoscopic and conventional sinus surgery.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is emerging as a valuable tool for the evaluation of specific conditions and diseases of paranasal sinuses. MRI has superior soft-tissue resolution compared with CT and is better at distinguishing fungal sinusitis, sinus neoplasms and intracranial extension of sinus disease (Kuhn, 1986) other important feature is the avoidance of ionic

irradiation, which is particularly significant for children. There are several limitations of MRI, however. Resolution of bony landmarks is poor, and therefore MR has a limited value in planning endoscopic sinus surgery. Other limitations include the high cost, the smallness of the machine portal (claustrophobia), and the need for sedation of most young children due to the long imaging times (Diament, 1992).

Ultrasonography

The role of ultrasound (US) in the evaluation of sinusitis remains unclear despite a growing experience with this technique. A-mode ultrasound, the most commonly used modality for sinusitis, emits sound waves along the axis of the transducer and produces a 2 dimensional scan that is displayed on an oscillometer (Rohr et al., 1986). The transducer is placed directly over either the maxillary or frontal sinus during testing. The locations of the ethmoid and sphenoid sinuses prohibit examination with ultrasound. The sound waves produced transmitted by fluid but reflected at tissue interface such as bone and fluid or bone and air (Kuhn, 1986). Use of the technique to diagnose sinusitis has met with variable success (Kuhn, 1986; Rohr et al., 1986; Landman, 1986). Ultrasound appears to detect moderate fluid in the maxillary sinus, but its capacity in diagnosing mucosal thickening is limited. In one series the low sensitivity of ultrasound led the authors to revise that a negative scan should be followed by radiographs if clinical suspicion were high (Rohr et al., 1986). Current ultrasound is not widely used for evaluating sinuses in the United States but is common in Europe. However continued evaluation of this modality is probably warranted as it is a noninvasive technique, is inexpensive, does not expose the patient to ionizing radiation

and require minimal patient cooperation particularly in case of maxillary sinusitis (Lichtenstein et al., 1998).

Medical management:

Acute sinusitis – Adults

The primary treatment of acute sinusitis in adults involves antibiotic therapy and decongestants (Axelsson et al., 1972; Aust et al., 1974; Stafford, 1990). Use of mucolytic agents, nasal irrigation, antral lavage, and either topical or systemic steroids usually decided on a case-by-case basis.

Antibiotic therapy is the primary treatment of acute bacterial sinusitis despite 40% of cases spontaneously resolving (Wald, 1992). Antibiotics are felt to facilitate recovery from acute episode, to prevent complications of sinusitis, and to prevent progressive mucosal changes that could result in chronic sinusitis. The efficacy of antibiotics in the treatment of sinusitis has been well-documented (Bamberger, 1991). Evans et al. (Evans et al., 1975) found antibiotics useful if the organism was sensitive to the agent being used. Carenfelt and Lundberg (Carenfelt et al., 1976) showed that bacteriocidal and bacteriostatic antibiotics are equally effective, provided the concentration reached in the sinus secretions exceeds the minimum inhibitory concentration for the bacteria isolated.

Antibiotic selection in acute adult sinusitis is most often emperic as nasal cultures are unreliable and maxillary sinus aspiration is unnecessary and not performed in most uncomplicated cases. Duration of therapy should be at least 7 to 10 days, but a minimum of 14 days and even longer if clinically

indicated has been advocated. In adults, amoxicillin, ampicillin, ceclor, cefuroxime axetil, trimethoprim-sulfamethoxazole, and clarithromycin (Karma et al., 1991; Dubois et al., 1993) have all proved clinically effective (Malow et al., 1989). The choice of a particular agent depends on several factors including history of drug allergies, cost, prior tolerance to the drug, and the incidence of β -lactam-producing organisms in a particular geographic area (Maresh et al., 1940). In particular, β -lactam-producing strains of Hemophilus influenzae and Branhamella catarrhalis can be problematic if ampicillin or amoxicillin are employed. However both ampicillin and clavulonate appear to be effective in irradicating most B-lactamase producing H. influenzae (Karma et al., 1991).

The antibiotic chosen should be given in sufficient dose to reach the minimum inhibitory concentration of likely pathogens within the sinus secretions. Eneroth and Lundberg (1976) studied antibiotic levels achieved in the sinus mucosa and secretions with ordinary clinical doses of penicillin and tetracycline. They found adequate levels in only 45% of patients treated with penicillin, whereas 93% of patients treated with teteracycline achieved adequate levels. They noted that an adequate level in the secretions ensured an adequate mucosal level. These findings were confirmed by Carenfelt et al. (1975) while studying penicillin, azidocillin, tetracycline, and doxycycline. They found that when antibiotic levels failed to reach the minimum inhibitory concentration for the bacteria isolated, bacterial growth was present in almost all samples aspirated 2 to 3 days after initiation of therapy. When the levels exceeded the minimum inhibitory concentration, eradication of bacteria occurred in 50% of cases. A similar study performed by Reynolds, Catlin and Cluff (Reynolds et al., 1964) found that

86% of patients responded within 14 days if treated with a correct antibiotic as compared to 65% treated with an incorrect or no antibiotic.

In most cases of sinusitis, decongestants play an important ancillary role in therapy. Decongestants are ∝- adrenergic drugs that produce vasoconstriction and may be administered topically or systemically. Use of topical decongestants should be limited to 5 days or less to minimize the risk of rebound rhinitis (rhinitis medicamentosa). Beyond 5 days, decongestant therapy should consist of a systemic preparation. There are two commonly available systemic decongestants – pseudoephedrine and phenylpropanolamine. While effective in reducing nasal congestion, these medications may produce undesirable stimulation of the central nervous system and cardiovascular system. Blood pressure elevation in patients with labile hypertension can occur with use of these drugs although the risk of inducing hypertension in otherwise normal subjects is minimal (Mabry, 1990). Because of their potential stimulatory effect, it is prudent to administer the evening dose of a decongestant several hours before bedtime or reduce the evening dose to avoid insomnia. Use of anti-histamines in the treatment of acute purulent sinusitis is not advised as thickening of mucous secretions may further inhibit sinus drainage and ventilation.

It may be helpful to include a mucolytic agent in the treatment program to decrease the tenacity of the mucus. Numerous preparations have been promoted for this purpose ranging from chicken soup and horse-radish to a variety of medications. Iodide preparations increase ciliary action, split mucoproteins, and possibly stimulate fibrin breakdown. However, documentation of the value of a saturated solution of potassium iodine (SSKI) is essentially anecdotal. Organic iodine, however, has been shown

to be an effective mucolytic and expectorant in patients with bronchitis, although its role in treating sinusitis is less well established. Guafenesin, another mucolytic agent, is frequently used in the management of sinusitis (Ziment, 1991). Unfortunately, guafenesin acts as an emetic in large doses and has a low therapeutic ratio. Therefore patients may experience gastrointestinal side effects from this preparation when used in appropriate dosages.

In many patients with sinusitis, great benefit is derived from regular saline irrigations delivered with a bulb syringe or nasal irrigator (Druce, 1990). Saline irrigations help to move thickened secretions through the nasal cavity. To be effective, the irrigations must be thorough and must be performed several times per day.

It may, on occasion, become necessary to use a nasal steroid aerosol to achieve maximum reduction of edema in the area of the osteomeatal complex, especially when allergy is a precipitating factor (Stafford, 1990). In theory, one should initiate antibiotic therapy well before adding topical steroids because steroids may inhibit the natural defense mechanisms of the sinuses. Further-more, nasal aerosol steroids are only effective if they reach the area of sinus drainage. Obstacles to the accurate placement of nasal steroid preparations include anterior nasal edema, polypoid disease in the nose, or septal deviation with hypertrophy of the inferior turbinates. Moreover, several days of treatment with topical nasal steroids are required before a clinical effect is noted and the maximum benefit is achieved only after 1 to 2 weeks of treatment. For these reasons, the benefit of nasal aerosol steroids in sinusitis should be questioned and in some opinion is contraindicated. However, if nasal steroids are to be used, there are several preparations

available to select from including beclomethasone (Mabry, 1991), flunisolide, and triamcinolone (Storms, 1991).

It has been suggested that, occasionally, the treatment of bacterial sinusitis will necessitate the use of systemic steroids to improve the clinical response to therapy, particularly if the condition is proving refractory to conventional therapy. It is our belief that this should very rarely be considered and it may be frankly contraindicated in the presence of fulminant infection.

Antral lavage is indicated for patients with acute sinusitis who have proved refractory to 3 to 5 days of antibiotics with increasing discomfort and in those patients who are at risk for opportunistic infection where the rapid identification of a specific pathogen and its pattern of drug susceptibility is crucial to a favorable outcome.

Acute sinusitis – Children

Treatment of acute sinusitis in the pediatric population consists of antimicrobial therapy, decongestants, and, rarely, simple maxillary sinus puncture and irrigation (Lusk et al., 1989; Wald, 1992). A variety of antimicrobials are available, which provide adequate coverage of the likely pathogens of acute sinusitis, and include amoxicillin, erythromycin, sulfisoxasole, trimethoprim, sulfamethoxasole, Ceclor and Augmentin. In choosing an antibiotic, one must again consider the patient's history of drug allergies, potential side effects, previous antibiotic treatment, and the increased prevalence of β-lactamase-producing strains of H. influenzae and M. catarrhalis, which are resistant to amoxicillin and ampicillin. While M. catarrhalis is rarely pathogenic in adults, it is responsible for approximately 20% of acute bacterial sinusitis in young children (Wald, 1992).

In an uncomplicated case of maxillary sinusitis, initial therapy with amoxicillin for 10 to 14 days is reasonable. Failure to demonstrate clinical improvement over 48 to 72 hours should prompt selection of an alternative antibiotic that covers β-lactam – positive organisms. Improvement, but no resolution, of symptoms after 10 to 14 days of therapy requires continuation of the antibiotic until all symptoms have resolved (Wald, 1992).

While decongestants or antihistamines are often employed as adjuvant therapy in children with sinusitis, the effectiveness of these preparations has not been adequately studied (Wald, 1992). As discussed previously histamines may have a deleterious effect by increasing the tenacity of secretions and are not recommended. While maxillary sinus irrigation and drainage dramatically improve symptoms in acute sinusitis, it is not used routinely in pediatric patients as antimicrobial therapy is usually adequate for acute sinusitis and puncture often requires either intravenous sedation or a general anesthetic in the pediatric population, especially in young children (Wald, 1992). Antral lavage, however, plays a role in symptomatic children who fail to respond to medical therapy or who have a threatening complication of sinusitis. Much like the adult, immunocompromised children may require early sampling of maxillary sinus contents to determine a specific pathogen because they are at increased risk.

Chronic sinusitis – Adults

Compared to acute sinusitis, the role of medical therapy in the treatment of chronic sinusitis is of little value. Chronic sinus infection is a sequelae of persistent sinus obstruction, the underlying cause of obstruction must be addressed (Lanza, 1992). Prolonged antibiotic therapy, decongestants and topical

nasal steroids, and even immunotherapy (if allergy is felt to be a causative factor), constitute the basic medical regimen used in chronic sinusitis. The microbiology of chronic sinusitis in adults differs from the acute process in that anaerobes or a mixture of aerobes and anaerobes are recovered frequently in chronic infection (Malow, 1989; Brook, 1994). Antibiotics used to cover anaerobes, such as penicillin VK or clindamycin are the appropriate choice for the treatment of chronic sinusitis. However, a recent study of chronic sinusitis in adults revealed that 44% of anaerobic isolates are β-lactamase positive (Brook, 1992). In these cases, penicillin would be ineffective and Augmentin or clindamycin are preferable (Brook et al., 1994; Brook et al., 1996). Minimum duration of antibiotic therapy in chronic sinusitis is 4 weeks. Decongestants, as always described, may be of some value.

Topical nasal steroids such as beclomethasone would be beneficial in chronic sinusitis especially if allergy is a predisposing factor. Unfortunately, the role of the steroids has not been well defined for chronic sinusitis.

Immunologic therapy is appropriate for a patient with chronic sinusitis with underlying allergy. It is an adjunctive treatment and not a substitute for the medical or surgical treatment. While safe and sensitive, immunotherapy routinely requires 6 months treatment before a clinical benefit is noted (Evans, 1992).

Chronic sinusitis – Children

The medical management of subacute and chronic sinusitis in children is, in general, similar to treatment in adults. A prolonged course of antibiotic therapy and systemic or topical

decongestants as well as topical nasal steroids and appropriate immunotherapy form the cornerstones of treatment of chronic pediatric sinusitis. Selection of an appropriate antibiotic must be done carefully for several reasons. While the microbiology of subacute pediatric sinusitis is similar to acute sinusitis (Wald et al., 1989), anaerobic bacteria are commonly found in chronic sinusitis (Brook, 1981). In addition, most children with chronic sinusitis have failed previous antibiotic regimens and one can anticipate a high rate of β-lactamase- producing pathogens in this setting (Wald, 1989). Tinkelman and Silk (Tinkelman et al., 1989) advocate maxillary sinus puncture early in the workup of children with chronic sinusitis to ensure the effectiveness of the antibiotic chosen.

As with adults, decongestants are commonly used in pediatric chronic sinusitis to decrease nasal congestion and promote sinus ventilation. In addition, topical nasal steroids play a role in the treatment of allergy-based nasal congestion because of their anti-inflammatory effects.

In children with immunodeficiency syndromes, immunotherapy in the form of immunoglobulin replacement or adjuvant therapy may be helpful in controlling refractory sinusitis (Polmar, 1992; Ramesh et al., 1997).

Surgical treatment of chronic sinusitis

The pathogenesis of chronic sinusitis involves ostial obstruction of the sinuses with secondary bacterial infection. As such, the role of surgery in chronic sinusitis is to reestablish sinus ventilation and drainage and allow for gradual resolution of mucosal disease (Kennedy, 1990). Patients who fail comprehensive medical therapy, with demonstrated abnormalities

of the osteomeatal complex on endoscopy and CT scan are candidates for surgical intervention (Kennedy, 1990; Richtsmeier, 1992). In addition, patients with intracranial or intraorbital complications of sinusitis will require drainage of the involved sinuses together with the surgical treatment of the complication. At present, "FESS" (Fibre-optic Endoscopic Sinus Surgery) is the "Golden Standard" (Eloy et al., 1997).

The surgical management of chronic sinus disease in children is controversial. Multiple surgical approaches have been advocated including endoscopic sinus surgery, adenotonsillectomy, and inferior meatal antrostomy. The value of each of these approaches is a matter of debate. While an association exists between adenoid and tonsil disease and sinusitis, the precise relationship remains unclear. Specific indications for adenotonsillectomy in the management of chronic sinusitis, unfortunately, do not exist (Lusk, 1992), but it stands to reason that if these are grossly enlarged or repeatedly infected, surgical removal is appropriate (Vandenberg et al., 1997). The role of endoscopic sinus surgery in the pediatric population is controversial but appears appropriate for patients with chronic recurring sinusitis (Wolf et al., 1995). Specific indications for surgery include true chronic sinusitis refractory to comprehensive medical therapy, suppurative complications of sinusitis, and serious underlying disease aggravated by recurrent sinusitis (Manning, 1992).

Treatment of fungal sinusitis

The management of both noninvasive and invasive fungal sinusitis is primarily surgical and involves debridement of diseased tissues and drainage of the involved sinuses. Noninvasive fungal sinusitis most commonly involves the

maxillary sinus and is treated by surgical debridement using either a standard Calwell-Luc approach (Corey et al., 1990) or newer endoscopic techniques (Stammberger, 1985). In these cases the fungal ball is curetted out and no bone need be removed. Usually, antifungal chemotherapy is not indicated. Invasive fungal sinusitis can be life–threatening and requires both aggressive surgical debridement and immediate antifungal chemotherapy (Parnes et al., 1989; Corey et al., 1990). In fact, in high-risk patients such as immunosuppressed patients, facial pain associated with abnormal sinus radiographs may even prompt empiric antifungal and antibacterial therapy (Kavanagh et al., 1991). Allergic fungal sinusitis is treated by surgical drainage of the involved sinus and systemic antifungal medications in some cases (Kupferberg et al., 1997). However, use of either intranasal steroids (Allphin et al., 1991) or systemic steroids (Corey, 1992; Kupferberg et al., 1997) seems to prevent recurrence of this condition. Duration of systemic steroid therapy is empiric currently but usually entails a tapering dose over several months (Corey, 1992). Mabry (Mabry et al., 1998) advocates the use of a combination of surgery followed by immunotherapy, employing fungal and antifungal antigens to which hypersensitivity has been demonstrated in the patient.

SINUSITIS AND BRONCHIAL ASTHMA

The relationship between the occurrence of sinusitis in asthmatic patients and the worsening of their asthma symptoms had been a matter of debate for many decades.

In his early article, Gottlieb (1925) proposed four possible mechanisms for this presumed relationship between sinusitis and asthma: 1) dripping of infected material into the pharynx leading to infection of pharynx and trachea, 2) an allergic reaction to the absorbed products of the bacterial infection, 3) mouth breathing of cold, dry air, and 4) stimulation of a nasobronchial reflex.Some of the more recent articles that studied these diseases did not agree on the pathogenetic relation of occurrence of both diseases together.

Some authors (Phipatanakul and Slavin, 1974; Slavin et al., 1983; Mings et al., 1988) have reported improvement in the overall management of series of adult asthmatic patients with chronic sinusitis following sinus surgery. Other authors (Friedman et al., 1984; Rachelefsky et al., 1984) have noted improvement in asthma management in small series of pediatric patients when chronic sinusitis was successfully treated medically. These authors have implicated a causal link between sinusitis and asthma but others contend that the two are merely associated as manifestations of respiratory mucosal inflammation secondary to antigen stimulus (Slavin, 1988; Zimmerman, Gold, 1991).

Cummings et al. (1983) in a double-blinded study with 42 asthmatic children with radiographic sinusitis showed that successful medical treatment of sinusitis improved asthma management compared with placebo-treated control group. This study also fails to prove a causal link between sinusitis and asthma as the antibiotics and inhaled steroids used in the treatment group may have had direct impact on patients' pulmonary disease. Besides that, the classic proposals that sinusitis may be causally linked with asthma via direct bacterial seeding or due to a nasosinobronchial reflex or diminished - adrenergic tone have not withstood some investigative studies (Settipane and Chafee, 1977; Schumacher et al., 1986; Bardin et al., 1990).

McFadden (1986) has pointed out that studies of the relationship between sinusitis and asthma are hampered by the tendencies of both disease processes toward spontaneous exacerbations and remissions. Slavin in 1992 stated that possible mechanisms for the cause-and-effect relationship between sinusitis and asthma include the eosinophil acting as an effector cell, inflammatory mediators and a vagal reflex.

However, as evidence has mounted that the principal pathogenic mechanism of most pediatric asthma involves antigen-triggered respiratory mucosal inflammation (Harlin et al., 1988; Adinoff and Cummings, 1989; McFadden and Gilbert, 1992), the role of the nose in filtering air takes on added significance (Druce and Slavin, 1991; Kaliner and Lemanske, 1992).

Impaired mucociliary clearance during acute or chronic sinusitis may exacerbate asthma by increasing the antigen load to bronchial mucosa (Manning et al., 1994).

Earlier on, Herrera and deShazo (1990) reported that the contribution of sinusitis to the induction and exacerbation of asthma is still unresolved. However, sinusitis appears to be an important underlying trigger for some cases of asthma and, therefore, should be suspected any time that acute or chronic asthma is difficult to control.

In an interventional study done by Manning et al. (1994) 14 steroid-dependent asthmatic patients with computed tomographic evidence of chronic sinusitis underwent endoscopic sinus surgery, following the surgery, 11 of the patients (78.5 %) demonstrated marked improvement in asthma management.

In another interventional study of 24 asthmatic pediatric patients who had been subjected to Fibre-optic Endoscopic Sinus Surgery (FESS) there was a surprisingly positive rate of improvement in asthmatic symptomatology, this finding attests to the long-recognized link between sinusitis and asthma. Patients with these two disorders must have therapy aggressively directed at the infectious etiology. When maximal asthmatic therapy is given without regard for the inflammatory sinus disease, suboptimal results will be obtained. However, when optimal therapy is directed toward the infectious condition, the asthma shows a dramatic response (Parsons and Philips, 1993).

In Egypt, Ibrahim and El-Atrebi (1990) conducted a study to determine the effect of surgical treatment of chronic maxillary sinusitis, in a small group of pediatric asthmatic patients (10 patients), on the outcome of asthma management among these patients. They found that the frequency of asthma attacks and the need for heavy medication have greatly diminished postoperatively in all patients.

A second similar study done by Badr-El-Din and El Khattib (1999) concluded that limited Fibre-optic Endoscopic Sinus Surgery (FESS), performed on 14 pediatric asthmatic patients suffering from chronic rhinosinusitis, was helpful in alleviating most of the allergic symptoms.

SUBJECTS AND METHODS

One hundred asthmatic Egyptian children aged from 7 to 15 years (50 boys and 50 girls), with different severities of asthma, had been selected from the Pediatrics Department (outpatient and inpatient) of Al Mattariah Teaching Hospital – Cairo during the period from January 1995 till end of April 1996. They were divided into three distinct groups (mild, moderate and severe) according to the degree of severity of their asthma.

The degree of severity of asthma was determined according to the following criteria (Guidelines 1, 1991):

Chronic mild asthma

1. Intermittent brief symptoms of asthma <2 times per week.
2. Exacerbations brief <1 hour.
3. No symptoms between exacerbations.
4. Spirometry normal when asymptomatic.
5. Peak flow varies less than 20% with symptoms.

Chronic moderate asthma

1. Symptoms >2 times per week.
2. Exacerbations may last days.
3. Occasional nocturnal symptoms.
4. Peak expiratory flow rate may be as low as 60%-80% of predicted.
5. Peak flow varies 20%-30% when symptomatic.

Chronic severe asthma

1. Continuous symptoms in spite of therapy for moderate asthma.
2. Limited activity level.
3. Frequent exacerbations and nocturnal symptoms.
4. Occasional emergency room visits or hospitalization.
5. Peak expiratory flow rate <60%.
6. Peak flow increases >30% with inhalation of bronchodilators.

All patients were assessed by full medical history and clinical examination and had undergone the following tests:

1. Plain radiography of chest:
Antero-posterior or postero-anterior views (according to the age of the patient).

2. Plain radiography of para-nasal sinuses:
Occipito-mental and lateral views mainly.

3. Peak expiratory flow rate (PEFR):
Peak expiratory flow rate is the greatest flow obtained on forced expiration after complete inspiration to total lung capacity.

Peak flow meters and PEFR measurements are useful in asthma management. They are simple to use, and the equipment is inexpensive and portable. Peak flow rates are effort dependent and measure mostly large airway function. PEFR correlates well with FEV_1 (Lawlor, Tashkin, 1995).

PEFR was recorded for every patient using the Mini-Wright peak flow meter as follows:
- The mouth piece was fitted to the peak flow meter.
- The pointer was set to zero on the scale.
- The peak flow meter was held so that the fingers are clear of the scale and slot, so not to obstruct the holes at the end of the peak flow meter.
- The patient was instructed to stand up. To take a deep breath, to place the peak flow meter in the mouth and holding it horizontally, closing the lips around the mouth piece, then to blow as hard and as fast as he could.
- The number on the scale indicated by the pointer was noted.

- The pointer was returned to zero and the procedure was repeated twice more to obtain three readings.
- The highest reading was recorded.

The PEFR was recorded twice for every subject, one time when the patient was free from the effect of medications (treatment stopped for at least 4 days) mostly on the same day of performing the skin sensitivity test. Another time, when the patient was under bronchodilation and therapeutic control of his asthma.

4. Skin sensitivity test:

Using the prick method.

It is a qualitative and quantitative test in which a drop of allergen extract is placed on the skin which is punctured in the dermal layer using a 1 mm. lancet.

The response is measured by a wheal-flare dermal reaction.

This is an immediate phase response mediated by histamine.

The magnitude of the response is measured as 0+ to 4+. A 4+ reaction is a large reaction including pseudopod extensions.

The test was done using the 10 most commonly used allergens for inhalant sensitivity skin testing in Egypt (El Heneidy et al., 1989; Zedan et al., 1990; Abou El Magd et al., 1991; Sultan et al., 1992).

The 10 allergens and the positive control with histamine (to judge the reactivity of the skin and to detect interfering anti-histamine mediators) were product of Miles Inc. – Pharmaceutical division – Elkhart, I.N. 46515 U.S.A.. A negative control with normal saline solution (to detect dermographism in the patient) was also used.

The aero-allergens used in the test were:

1- Ryegrass Mix GIP.

2- Aspergillus Mix.
3- Penicillium Mix.
4- House dust Mix.
5- Feather Mix.
6- Wool, sheep.
7- Black fly.
8- Cockroach Mix.
9- Standardized Mite of Dermaphagoides Farinae.
10- Standardized Mite of Dermaphagoides Pteronyssinus.

5. Complete blood count:
Including differential leucocytic count to detect eosinophilia.

6. Total serum IgE determination:
Determined using Enzyme-Linked Immunosorbent Assay (ELISA).

Principle of the test:
The Genzyme Diagnostics IgE Quantitative Test is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle (Engvall, 1980; Uottla et al., 1981). The test specimen (serum) is added to the anti-IgE monoclonal antibodies immobilized on polystyrene microwells (solid phase) and incubated with the Zero Buffer. If human IgE is present in the specimen, it will bind to the antibodies on the well. The well is then washed to remove any residual test specimen, and goat anti-IgE in the antibody-enzyme (horseradish peroxidase) conjugate reagent is added. The conjugate reagent will bind immunologically to the IgE on the well, resulting in the IgE molecules being sandwiched between the solid phase and the enzyme-linked antibodies. After an incubation at room temperature, the solid phase is washed with water to remove

unbound labeled antibody. A solution of 3,3',5,5'-Tetramethylbenzidine (TMB) is added and incubated for 15 minutes, resulting in the development of a blue color. The color development is stopped with the addition of Stop Solution and the resulting yellow color is measured spectrophotometrically at 450 nm. The concentration of IgE is directly proportional to the color intensity of the test sample.

Materials provided with the Test Kit:

1. Antibody Coated Microwells (coated with mouse monoclonal anti-IgE), 96 wells.
2. Zero Buffer (Tris buffer with preservative and yellow dye), 13 ml.
3. Enzyme Conjuguate Reagent (goat anti-IgE conjugated to horseradish peroxidase), 18 ml.
4. Zero Standard, 3ml.
5. Reference Standards (0, 10, 50, 250, 500 and 1000 IU/ml of IgE in bovine serum with 0.1% sodium azide as preservative), 1ml. per vial.
6. Color Reagent A (Hydrogen peroxide in acetate buffer), 13 ml.
7. Color Reagent B (3,3',5,5'-Tetramethylbenzidine (TMB) in methanol (<50%), DMSO (<2%) and glycerol (>15%), 13 ml. To prepare TMB Substrate Reagent, mix equal parts of Color Reagent A with Color Reagent B in a clean glass container up to 2 hours before use. Store in the dark. Excess solution should be discarded after use.
8. Stop Solution (2 N hydrochloric acid), 10 ml.

Materials required but not provided

1. Distilled or deionized water.
2. Precision pipettes: 0.02, 0.1, 0.15, 0.2 and 1 ml.

3. Disposable pipette tips.
4. Glass tube or flask for preparing TMB Substrate Reagent.
5. Microwell reader (with bandwidth of 10 nm or less and an optical density range of 0 to 2 A or greater at 450 nm wavelength "A450" is acceptable)
6. Absorbent paper.
7. Graph paper.
8. Control sera (recommended).

Procedural notes:

1. Manual pipetting: it is recommended that no more than 32 wells be used for each assay run. Pipetting of all standards, samples and controls should be completed within 3 minutes.
2. Automated pipetting: a full plate of 96 wells may be used in each assay run. However, it is recommended that the pipetting of all standards, samples and controls be completed within 3 minutes.
3. All standards, samples and controls should be run in duplicate.
4. A standard curve should be run in each assay to ensure valid results.
5. It is recommended that the wells be read within 30 minutes following step 18.
6. If automated washing is used, wash with a minimum volume of 300 ul/well.

Assay procedure:

1. The desired number of coated wells is secured in the holder.
2. 20 ul of standards, samples and controls are dispensed into appropriate wells.
3. The plate is gently shaken for 30 seconds.
4. Two drops (100 ul) of zero buffer are dispensed into each well

5. The plate is thoroughly shaken for 10 seconds. It is important to have a complete mixing in this step.
6. Incubation at room temperature for 30 minutes.
7. The incubation mixture is removed by flicking plate contents into a suitable waste container.
8. The microwells are rinsed and flicked 5 times with running tap or distilled water.
9. The wells are sharply struck on absorbent paper to remove residual water droplets.
10. Three drops (150 ul) of Enzyme Conjugate Reagent are dispensed into each well. The plate is gently shaken for 5 seconds.
11. Incubation at room temperature for 15 minutes.
12. The incubation mixture is removed by flicking plate contents into a suitable waste container.
13. The microwells are rinsed 5 times with running tap or distilled water.
14. The wells are sharply struck on absorbent paper to remove residual water droplets.
15. 200 ul of TMB Substrate Reagent are dispensed into each well. The plate is gently shaken for 5 seconds.
16. Incubation at room temperature in the dark for 15 minutes.
17. The reaction is stopped by adding one drop of (50 ul) of Stop Solution to each well.
18. The plate is gently shaken for 5 seconds.
19. The absorbance is read at 450 nm (A450).

Calculation of results:

1. The mean absorbance values (A450) are calculated for the duplicate Reference standards, controls and patient samples.

2. Using graph paper, a standard curve is constructed by plotting the mean absorbance obtained for each Reference Standard against its concentration in IU/ml, with absorbance on the vertical (y) axis and concentration on the horizontal (x) axis.
3. Using the mean absorbance value for each sample, the corresponding concentration of IgE in IU/ml is determined from the standard curve. Computer data reduction can also be employed.
4. Any diluted samples must be converted by the appropriate dilution factor.

Interpretation of results:

1. Results of a typical standard run are shown below:

	A450 nm		
IgE (IU/ml)	1	2	Mean
0	0.022	0.026	0.024
10	0.135	0.135	0.135
50	0.528	0.576	0.552
250	1.506	1.514	1.510
500	1.976	1.944	1.960
1000	2.496	2.458	2.477

Figure 2: This standard curve covers a dynamic range from 5 to 1000 IU/ ml. IgE.

2. Standard Curve:

Note: this standard curve is for the purpose of illustration only, and should not be used to calculate unknowns. Each laboratory must provide its own data and standard curve.

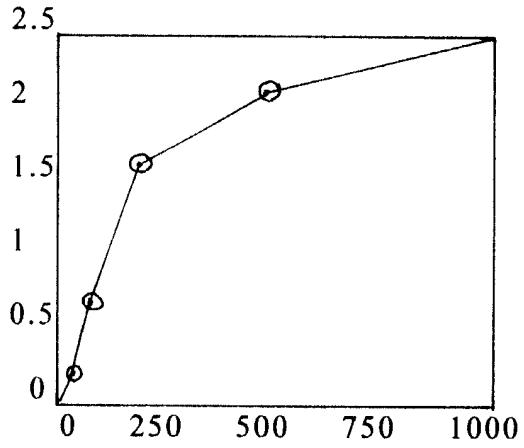


Figure 3: Ig.E Concentration (IU/ml.)

Expected values:

The total IgE level in normal, allergy-free adults is less than 150 IU/ml of serum. Variation in total IgE concentrations may be expected in certain age groups and clinical conditions.

Each laboratory should establish its own normal ranges based on patient population in the geographical areas served. These values have clinical significance only after a statistically significant number of assays have been performed over a suitable period of time.

The available literature provides the following information relative to total IgE in human serum (Berg, Johansson, 1969; Kjellman et al., 1976; Wilig et al., 1980; Barbee et al., 1981).

Normal geometric mean: 27.6 IU/ml IgE.

Normal ranges:

Age (years)	IgE (IU/ml)
0 – 3	<10
3 – 4	<25
4 – 7	<50
7 – 14	<100
15 +	<150

Quality control:

Good laboratory practice requires that low, medium and high controls are run with each calibration curve. A statistically significant number of controls should be assayed to establish mean values and acceptable ranges to assure proper performance.

Standardization:

Reference Standards are standardized against WHO 2nd. IRP, 75/502 (1981).

Limitations of procedure:

1. Reliable and reproducible results will be obtained when the assay procedure is carried out with a complete understanding of the package insert instructions and with adherence to good laboratory practice.

2. The results obtained by this test should be used only as an adjunct to other data available to the physician. IgE-mediated allergy should not be ruled out when the test results are low or normal, or implicated as the single source when the test results indicate elevated IgE levels. There are patients with elevated serum IgE levels who are free of allergic symptoms, as well as patients with allergic problems who have normal serum IgE level. Slight hemolysis and/or lipemia do not interfere with the assay.

The presence of sediment or precipitates in specimens or reagents may indicate contamination and those specimens or reagents should not be used.

The wash procedure is critical, insufficient washing will result in poor precision and falsely elevated absorbance readings.

Statistical analysis:

Statistical Analysis System was used for data management and analysis.

Harvard Graphics was used for drawing figures.

Quantitative data were summarized as means and standard deviations, qualitative data as percentages.

Comparisons between those with sinusitis and those free of sinusitis with respect to quantitative measurements were done using the Student's t-test. While comparisons between the different groups of bronchial asthma were performed by the analysis of variance procedures.

In the case of qualitative measurement, the chisquare or Fisher's exact test was used (Dixon and Massey, 1983).

RESULTS

The study included 100 known asthmatic Egyptian children (50 boys and 50 girls), their age ranged between 7 and 15 years with a mean of 9.9 years ± 2.1 S.D., the degree of their asthma severity was determined according to the criteria of the Guidelines for the Diagnosis and Management of Asthma, 1991. They were, then, divided into 3 groups of mild, moderate and severe asthma. The results of the study are illustrated in tables 6–23 and figures 4–12.

Table 6 shows the relation between the degree of severity of asthma and the age of the patients and the age of onset of asthma. There is no difference in the age of the patients in the 3 different groups of asthma severity (p= 0.607). But the age of onset of asthma in the mild asthmatic group (4.1 years ± 3.2 S. D.) is statistically significantly lower than in the moderate or severe asthma groups (5.8 years ± 2.4 S.D. and 5.7 years ± 2.6 S.D. respectively).

Table 7 shows the relation between the degree of severity of asthma and the gender among the studied asthmatic patients.

There is no statistically significant correlation between the severity of asthma and the gender of the patients, though there is a female preponderance in the mild asthma group (female: male ratio of 1.75:1) and a male preponderance in the severe asthma group (male: female ratio of 1.53:1) which denotes tendency of asthma to be more severe in males than in females among the studied age group of asthmatic children.

The distribution of allergic symptoms and relevant history among the studied asthmatic patients is illustrated in table 8. The most frequent history finding is parental smoking (28%) and the least frequent finding is allergic reaction to drugs (14%).

Table 9 shows the relation between the degree of severity of asthma and the allergic symptoms and relevant history among the studied asthmatic patients.
There is no statistically significant correlation between the mentioned allergic symptoms and the severity of asthma in the studied asthmatic patients. Though it can be noticed that family history of allergy is relatively most frequent in the severe asthma group (34.2%), parental smoking and reaction to drugs are relatively most frequent in the moderate asthma group(34.5% and 20.7% respectively), allergy to insect bites, presence of pets and reaction to food is relatively most frequent in the mild asthma group (24.2%, 27.3% and 18.2% respectively).

The distribution of clinical signs of allergy among the studied asthmatic patients is shown in table 10. The most frequent sign is skin allergy (46%), followed by allergic rhinitis (37%), and the least frequent sign is allergic conjunctivitis (17%).

The relation between the degree of severity of asthma and the clinical signs of allergy among the studied asthmatic patients is illustrated in table 11.
Allergic rhinitis is the only sign of allergy that is statistically significantly correlated with the severe asthma group (55.3%). Although skin allergy and allergic conjunctivitis are not statistically significantly correlated with the severity of asthma, yet they are relatively most frequent in the group of severe asthma among the studied patients (52.6% and 23.7%).

Table 12 shows the distribution of positive radiological findings and skin sensitivity test results among the studied asthmatic patients.

The most frequent is the positive skin sensitivity test (42%), followed by relevant chest x-ray findings (36%), then followed by positive x-ray findings of sinusitis (34%).

Table 13 and figure 4 show the relation between the degree of severity of asthma and the positive radiological findings and skin test results among the studied asthmatic patients.
There is a statistically significant correlation between the relevant chest x-ray findings (52.6%) and the x-ray findings of sinusitis (52.6%)and the severe asthma group.
Though the positive skin sensitivity test results are not statistically significantly correlated with the severity of asthma, yet it is relatively most frequent (52.6%) in the severe asthma group than in the other 2 groups.

The distribution of the identified allergens among the studied patients is shown table 14. House dust is the most commonly identified allergen on skin sensitivity testing (29%), followed by Aspergillus mix (12%) then Penicillium mix (11%) and least commonly identified is the black fly (1%).

Table 15 shows the percentage frequency of positive skin tests to some inhalant allergens in the studied asthmatic patients.
The house dust mix (69%) being the most commonly positive and the black fly (2.3%) the least commonly positive.

Table 16 and figures 6, 7 and 8 show the relation between the degree of severity of asthma and the P.E.F.R. without treatment and under treatment, eosinophilic count in blood and T.S. IgE level.
They are all statistically significantly correlating with the degree of severity of asthma: P.E.F.R. is lowest in the severe

asthma group (without treatment: 125 L./second ± 30.1 S.D. and under treatment: 190.7 L./second ± 44.8 S.D.) and the eosinophilic count and T. S. IgE level are most elevated in the severe asthma group (12.3% ± 7.6 S.D.and 304.8 I.U./ml. ± 255.7 S. D. respectively).

The relation between the presence of sinusitis and the degree of severity of asthma is illustrated in table 17 and figure 5.

There is a statistically significant correlation between the presence of sinusitis and the degree of asthma severity being more common in the severe group (54.8%) than in the moderate or mild groups (25.8% and 19.4% respectively).

Table 18 shows the relation between the presence of sinusitis and the age of the patients and the age of onset of asthma. There is no statistically significant correlation between the presence of sinusitis and the age of the patients and the age of onset of asthma.

Table 19 shows the relation between the presence of sinusitis and the gender of the patients among the studied asthmatic patients. There is no statistically significant correlation between the presence of sinusitis and the gender of the patients.

The relation between the presence of sinusitis and the allergic symptoms and relevant history among the studied asthmatic patients is shown in table 20. Family history of allergy is the only symptom that is statistically significantly correlating with the presence of sinusitis (48.4%).

Table 21 shows the relation between the presence of sinusitis and the clinical signs of allergy among the studied asthmatic patients. Allergic rhinitis is statistically significantly correlated with the presence of sinusitis (87.1%), while skin allergy (48.4%) and allergic conjunctivitis (25.8%) are not statistically correlated with the presence of sinusitis.

The relation between the presence of sinusitis and the positive radiological findings and positive skin test results among the studied asthmatic patients is illustrated in table 22 and figure 9. The relevant chest x-ray findings (61.3%), the x-ray findings showing signs of sinusitis (96.8%) and the positive skin test results (71.0%) are all statistically significantly correlated with the presence of sinusitis.

Table 23 and figures 10, 11 and 12 show the relation between the presence of sinusitis and the results of P.E.F.R. without treatment and under treatment, eosinophilic count (%) in blood and T.S. IgE level.

The presence of sinusitis is statistically significantly correlated with elevated eosinophilic count (17.4% $\pm$ 6.3 S.D.) in blood and elevated T.S. IgE level (384.5 I.U./ml. $\pm$ 264.7 S.D.). While there is no correlation between the lowered P.E.F.R. value and the presence of sinusitis among the studied asthmatic children ($p=0.053$ and $p= 0.138$).

Table 6: Relation between the degree of severity of asthma and the age of the patients and the age of onset of asthma.

Age (years)	Severity of asthma			P- value*
	Mild (n= 33)	Moderate (n= 29)	Severe (n= 38)	
Age	9.7±2.4	9.8±2.0	10.2±2.1	0.607
Age of onset	4.1±3.2	5.8±2.4	5.7±2.6	0.017

Values are means + standard deviations.
*P- value ⩽ 0.05 is considered significant.

Table 7: Relation between the degree of severity of asthma and the gender among the studied asthmatic patients.

Sex	Severity of asthma			P- value*
	Mild	Moderate	Severe	
Male (n= 50)	12(24%)	15(30%)	23(46%)	
Female (n= 50)	21(42%)	14(28%)	15(30%)	0.124

*P- value ⩽ 0.05 is considered significant.

Table 8: Distribution of allergic symptoms and relevant history among the studied asthmatic patients.

Symptom	percentage of cases (n= 100)	
Parental smoking	One parent	22
	Both parents	6
Family history of allergy		27
Allergy to insect bites		22
Presence of pets		21
Reaction to food		16
Reaction to drugs		14

Table 9: Relation between the degree of severity of asthma and the allergic symptoms and relevant history among the studied asthmatic patients.

Symptom	Severity of asthma			P- value*
	Mild (n= 33)	Moderate (n= 29)	Severe (n= 38)	
Parental smoking	9(27.3%)	10(34.5%)	9(23.7%)	0.617
Family history of allergy	5(15.2%)	9(31.0%)	13(34.2%)	0.166
Allergy to insect bites	8(24.2%)	6(20.7%)	8(21.0%)	0.930
Presence of pets	9(27.3%)	7(24.1%)	5(13.2%)	0.307
Reaction to food	6(18.2%)	4(13.8%)	6(15.8%)	0.894
Reaction to drugs	4(12.1%)	6(20.7%)	4(10.5%)	0.459

*P-value $\leq$ 0.05 is considered significant.

Table 10: Distribution of clinical signs of allergy among the studied patients.

Sign	percentage of cases (n= 100)
Skin allergy	46
Allergic rhinitis	37
Allergic conjunctivitis	17

Table 11: Relation between the degree of severity of asthma and the clinical signs of allergy among the studied asthmatic patients.

Symptom	Severity of asthma			P- value*
	Mild (n= 33)	Moderate (n= 29)	Severe (n= 38)	
Skin allergy	11(33.3%)	15(51.7%)	20(52.6%)	0.203
Allergic rhinitis	6(18.2%)	10(34.5%)	21(55.3%)	0.005
Allergic conjunctivitis	4(12.1%)	4(13.8%)	9(23.7%)	0.373

*P-value ⩽ 0.05 is considered significant.

Table 12: Distribution of positive radiological findings and skin sensitivity test results among the studied asthmatic patients.

Investigation	percentage of cases (n= 100)
Positive skin sensitivity test	42
Relevant chest x-ray findings	36
X-ray findings showing signs of sinusitis	34

Table 13: Relation between the degree of severity of asthma and the positive radiological findings and skin test results among the studied asthmatic patients

Investigation	Severity of asthma			P-value*
	Mild (n= 33)	Moderate (n= 29)	Severe (n= 38)	
Positive skin test	12(36.4%)	10(34.5%)	20(52.6%)	0.239
Relevant x-ray findings	6(18.2%)	10(34.5%)	20(52.6%)	0.010
X-ray findings showing signs of sinusitis	6(18.2%)	8(17.6%)	20(52.6%)	0.006

*P-value ⩽ 0.05 is considered significant.

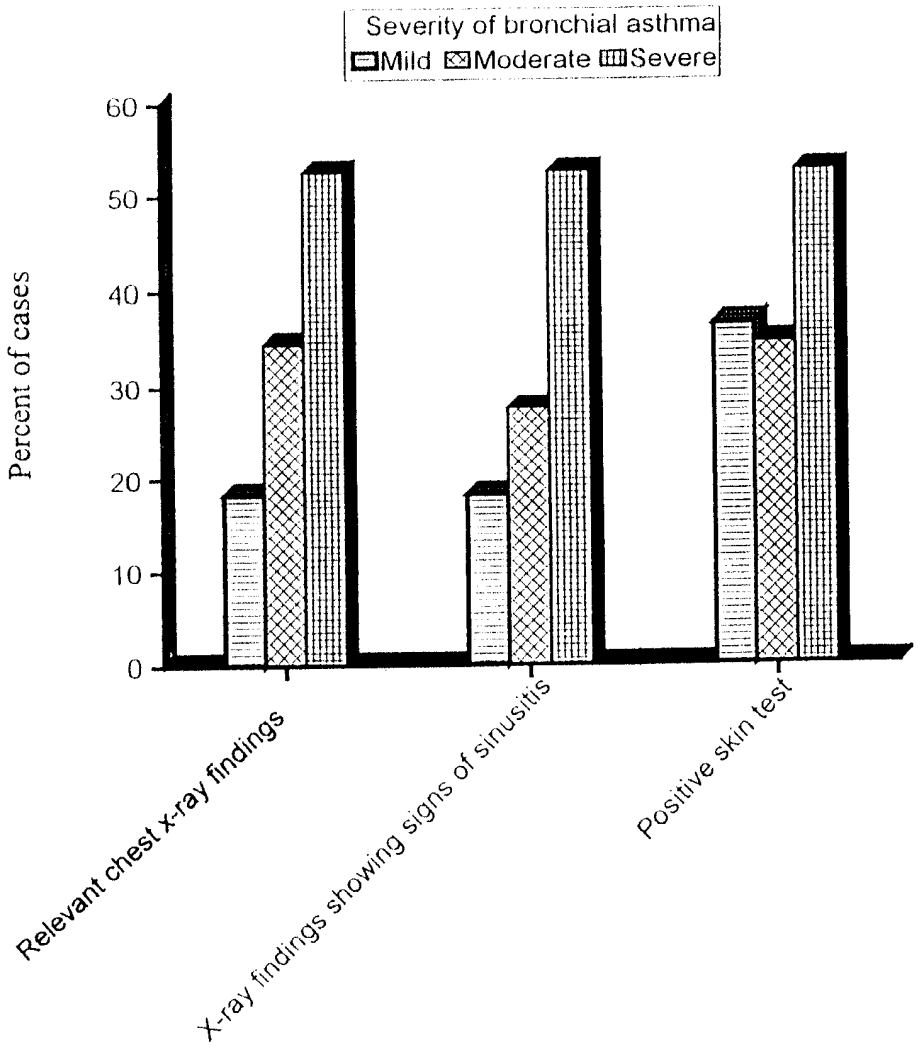


Figure 4: Relation between the degree of severity of asthma and the positive radiological findings and positive skin sensitivity tests among the studied asthmatic patients.

Table 14: Distribution of the identified allergens among the studied patients.

Inhalant allergen	Number of positive cases
House dust mix	29
Aspergillus mix	12
Penicillium mix	11
Feather mix	9
Dermatophagoides farinae	7
Dermatophagoides Pteronyssinus	7
Wool sheep	4
Ryegrass mix GIP	3
Cockroach mix	3
Black fly	1

Table 15: The percentage frequency of positive skin tests to some inhalant allergens in the studied asthmatic patients.

Positive skin sensitivity	Percentage from positive cases (n=42)
House dust mix	69
Aspergillus mix	28.5
Penicillium mix	26.2
Dermatophagoides farinae	16.6
Dermatophagoides pteronyssinus	16.6
Wool sheep	9.5
Feather mix	9
Ryegrass mix GIP	7.1
Cockroach mix	7.1
Black fly	2.3

Table 16: Relation between the degree of severity of asthma and the P.E.F.R. without treatment and under treatment, eosinophilic count in blood and T.S. IgE level.

Measurement#	Severity of asthma			P-value*
	Mild (n= 33)	Moderate (n= 29)	Severe (n= 38)	
P.E.F.R. without TTT.	231.5±55.1	79.0±38.2	125.5±30.1	<0.001
P.E.F.R. under TTT.	284.4±69.7	227.9±48.6	190.7±44.8	<0.001
Eosinophils %	6.4±5.1	0.4±7.4	12.3±7.6	0.002
T. S. IgE level	128.2±164.7	171.0±167.1	304.8±255.7	<0.001

Values are means + standard deviations, ranges in parentheses.
*P-value ≤0.05 is considered significant.
P.E.F.R. (L./second) . T.S. IgE level (I.U./ml.)

Table 17: Relation between the presence of sinusitis and the degree of severity of asthma.

Presence of sinusitis	Severity of asthma			P-value*
	Mild	Moderate	Severe	
Positive (n= 31)	6(19.4%)	8(25.8%)	17(54.8%)	
Negative (n= 69)	27(39.1%)	21(30.4%)	21(30.4%)	0.049

*P-value ≤ 0.05 is considered significant.

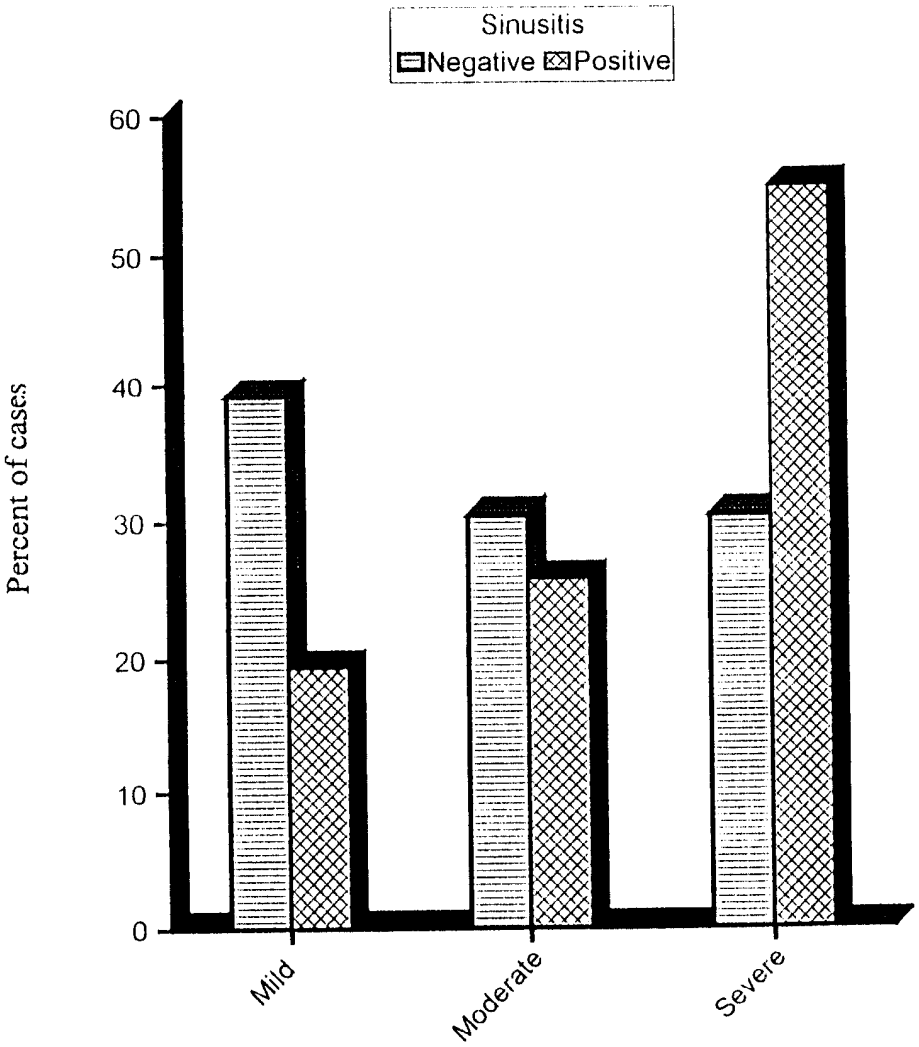


Figure 5: Relation between the presence of sinusitis and the degree of severity of asthma among the studied asthmatic children.

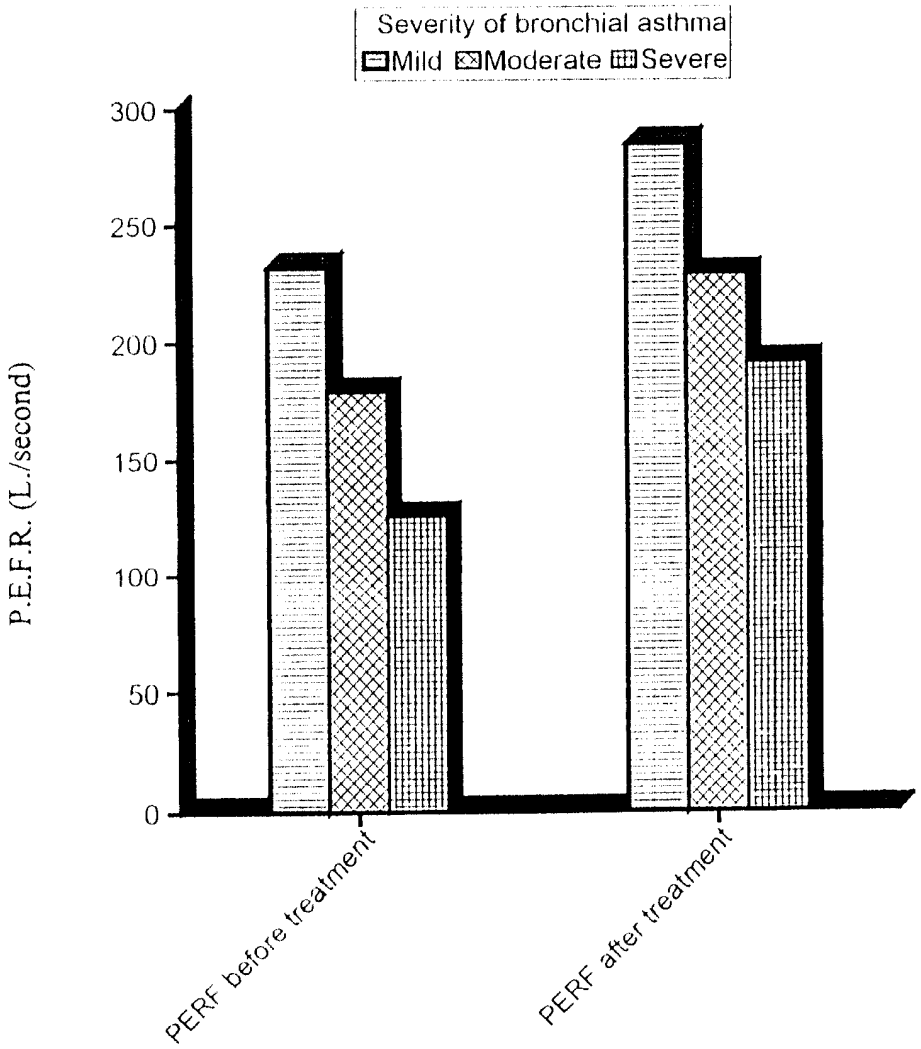


Figure 6: Relation between the degree of severity of asthma and the P.E.F.R. without treatment and under treatment among the studied asthmatic children.

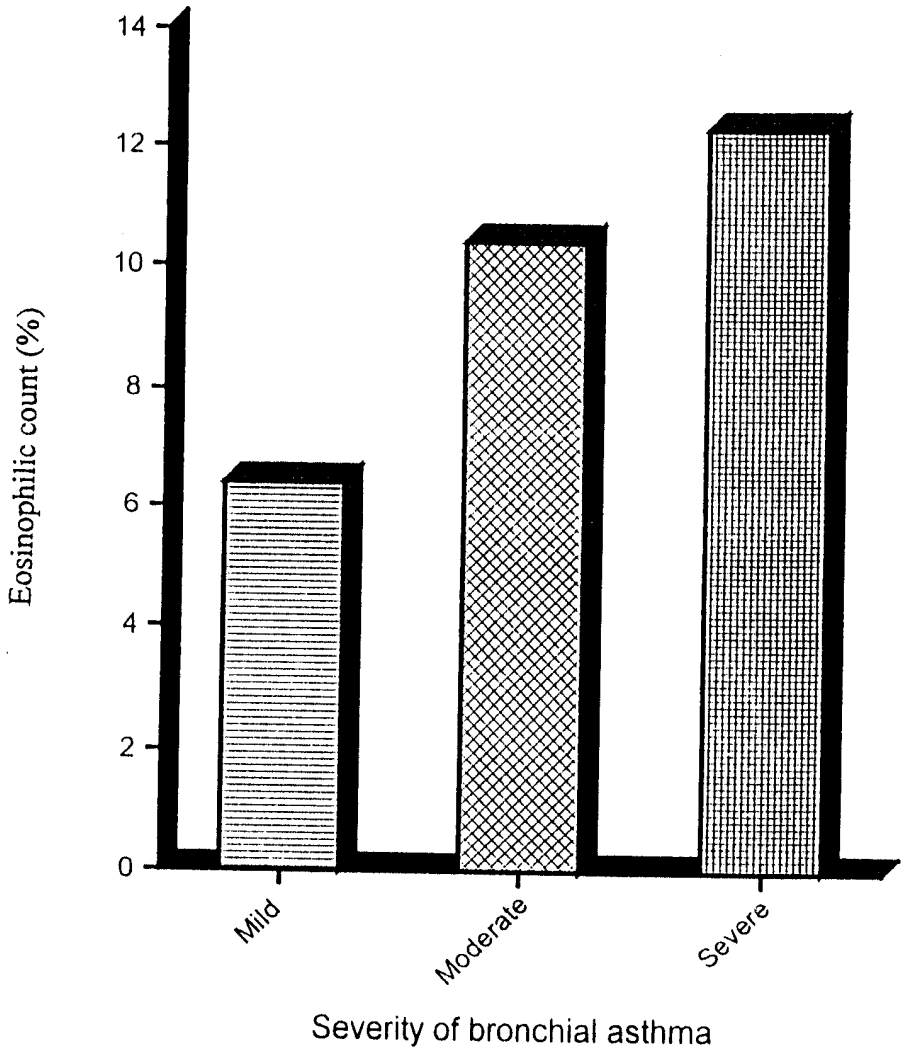


Figure 7: Relation between the degree of severity of asthma and the eosinophilic count (%) in blood among the studied asthmatic patients.

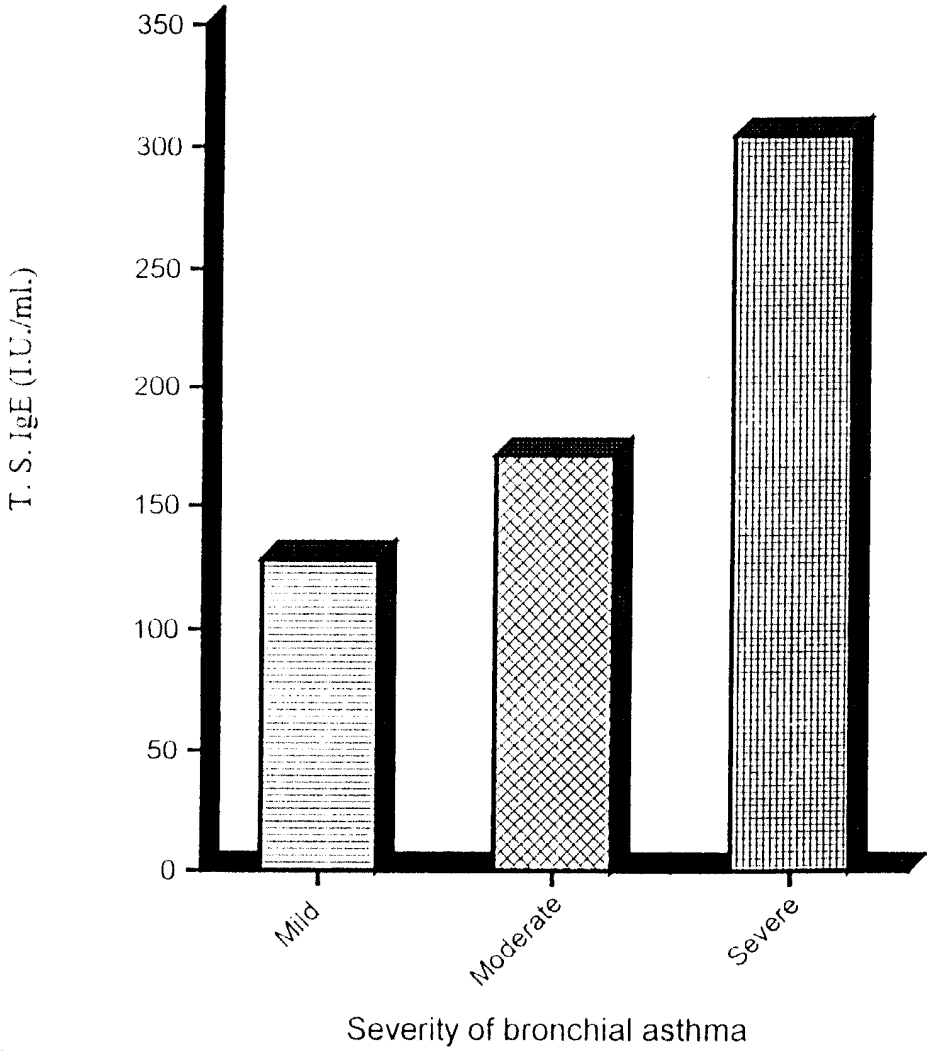


Figure 8: Relation between the degree of severity of asthma and the T. S. IgE level among the studied asthmatic patients.

Table 18: Relation between the presence of sinusitis and the age of the patients and the age of onset of asthma.

Measurement#	Presence of sinusitis		P-value*
	Positive (n= 31)	Negative (n= 69)	
Age (years)	9.8±2.1	10.0±2.3	0.780
Age at onset (years)	5.2±2.9	5.2±2.8	0.988

Values are means + standard deviations.
*P-value ⩽ 0.05 is considered significant.

Table 19: Relation between the presence of sinusitis and the gender of the patients among the studied asthmatic children.

Sex	Presence of sinusitis		P- value*
	Positive	Negative	
Male (n= 50)	17(34%)	33(66%)	0.517
Female (n= 50	14(28%)	36(72%)	

*P- value < 0.05 is considered significant.

Table 20: Relation between the presence of sinusitis and the allergic symptoms and relevant history among the studied asthmatic patients.

Symptom	Presence of sinusitis		P-value*
	Positive (n= 31)	Negative (n= 69)	
Family history of allergy	15(48.4%)	12(17.4%)	0.003
Allergy to insect bites	8(25.8%)	14(20.3%)	0.538
Parental smoking	6(19.4%)	22(31.9%)	0.197
Reaction to drugs	6(19.4%)	8(11.6%)	0.354
Presence of pets	4(12.9%)	17(24.6%)	0.288
Reaction to food	3(9.7%)	13(18.8%)	0.378

*P- value $\leqslant$ 0.05 is considered significant.

Table 21: Relation between the presence of sinusitis and the clinical signs of allergy among the studied asthmatic patients.

Sign	Presence of sinusitis		P- value*
	Positive (n= 31)	Negative (n= 69)	
Allergic rhinitis	27(87.1 %)	10(14.5 %)	< 0.001
Skin allergy	15(48.4 %)	31(44.9 %)	0.748
Allergic conjunctivitis	8(25.8 %)	9(13.0 %)	0.116

*P- value $\leqslant$ 0.05 is considered significant.

Table 22: Relation between the presence of sinusitis and the positive radiological findings and positive skin test results among the studied asthmatic patients.

Investigation	Presence of sinusitis		P- value*
	Positive (n= 69)	Negative (n= 31)	
X-ray findings showing signs of sinusitis	30(96.8%)	4(5.8%)	< 0.001
Positive skin test	22(71.0%)	20(29.0%)	< 0.001
Relevant x-ray findings	19(61.3%)	17(24.6%)	< 0.001

*P-value ⩽ 0.05 is considered significant

Table 23: Relation between the presence of sinusitis and the results of P.E.F.R. without treatment and under treatment, eosinophilic count (%) in blood and T.S. IgE level.

Measurements#	Presence of sinusitis		P- value*
	Positive (n= 31)	Negative (n= 69)	
P.E.F.R. without TTT.	158.4±59.0	183.9±60.9	0.053
P.E.F.R. under TTT.	217.4±63.8	239.1±68.6	0.138
Eosinophilic count (%)	17.4±6.3	6.4±4.5	< 0.001
T.S. IgE level	384.5±264.7	128.2±130.9	< 0.001

Values are means+standard deviations, ranges in parentheses.
*P- value ⩽ 0.05 is considered significant.
P.E.F.R. (L./second). T.S. IgE level (I.U./ml.).

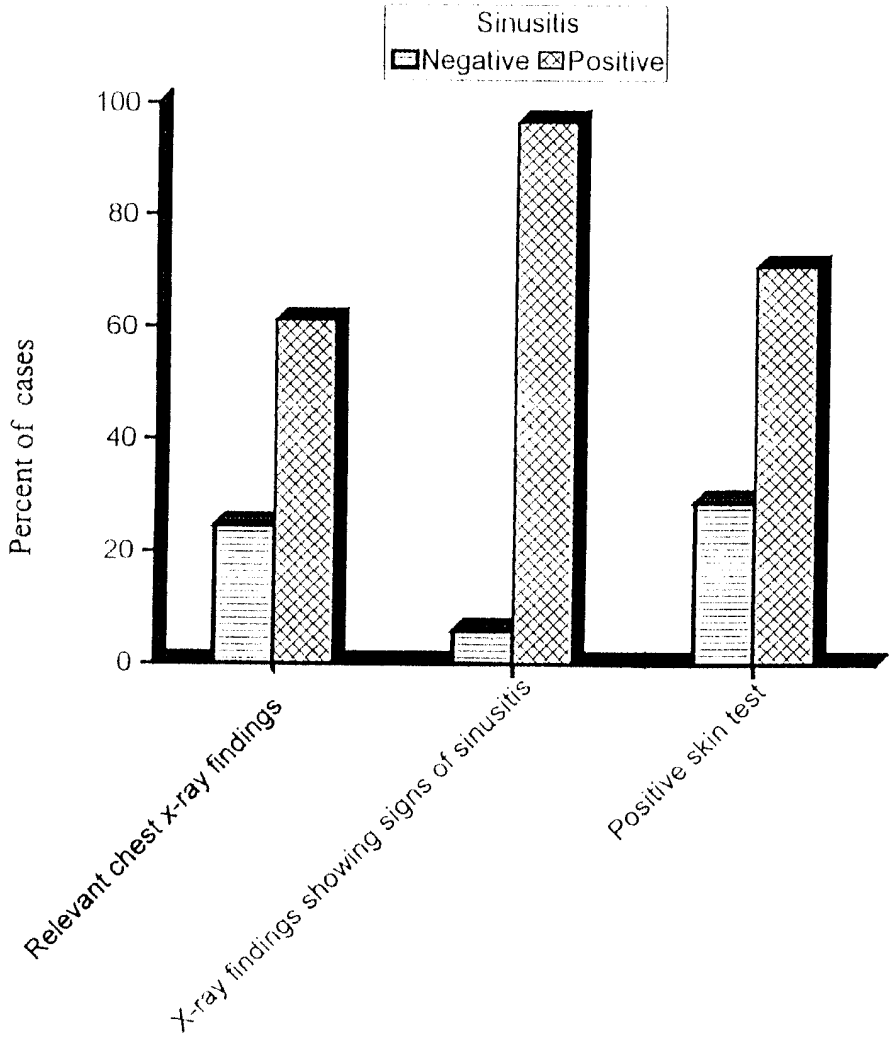


Figure 9: Relation between the presence of sinusitis and the positive radiological findings and positive skin sensitivity tests among the studied asthmatic patients.

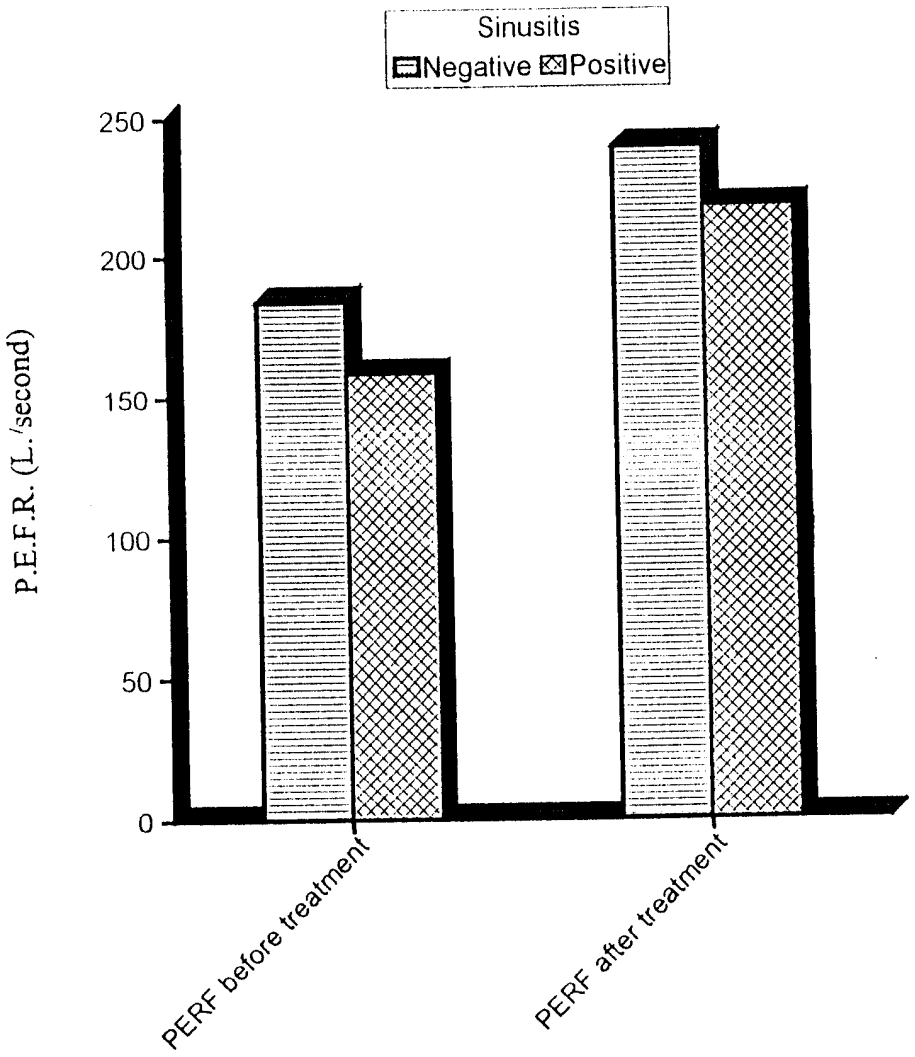


Figure 10: Relation between the presence of sinusitis and the P.E.F.R. without treatment and under treatment among the studied asthmatic children.

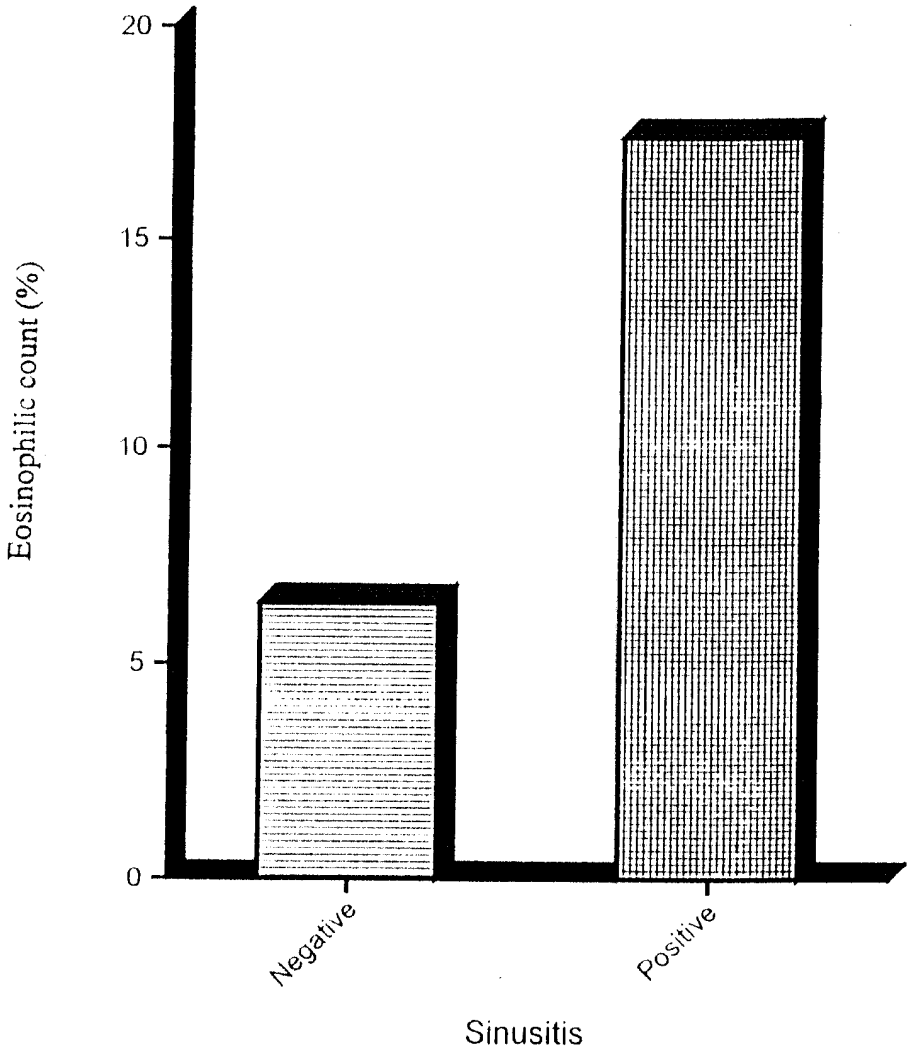


Figure 11: Relation between the presence of sinusitis and the results of eosinophilic count (%) in blood among the studied asthmatic children.

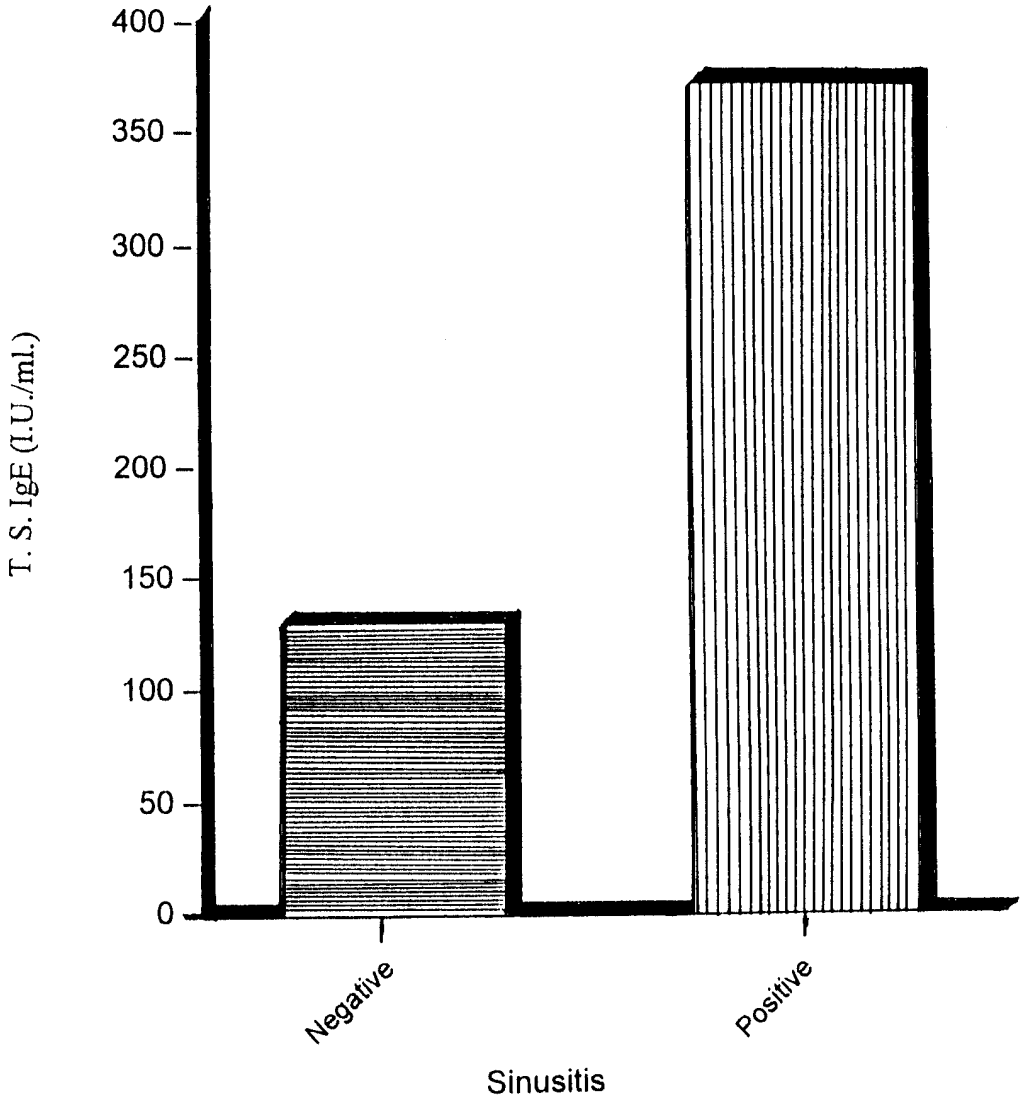


Figure 12: Relation between the presence of sinusitis and the T. S. IgE level among the studied asthmatic patients.

DISCUSSION

Bronchial asthma is a major health problem allover the world as well as in Egypt. The magnitude of the problem is increasing as it has been shown in studies from different parts of the world. Crater and Platts-Mills (1998) stated that the prevalence of asthma has dramatically increased among American school-aged children and young adults over the last 30 years. Epidemiological studies done in Egypt showed a rising trend in asthma prevalence, El Hefni et al. (1994) found a 8.2% prevalence of asthma among 3-15 years old children in Cairo while on 1995 Atef et al. reported a prevalence of 11.4% of asthma among 6-12 years old children in El-Salam area in Port-Said. Although the previously mentioned Egyptian studies were from different regions in Egypt yet it gives an indication that asthma is a growing health hazard in Egypt as in other parts of the world.

In addition, evidences are accumulating and are pointing to an increase in severity of asthma in many areas of the world, both in adults and in children (Buist, Vollmer, 1990; Grant et al., 1999).

The reasons for the increase in prevalence, morbidity and mortality are not clear. Possible explanations include increases in outdoor air pollution, increases in indoor air pollution because energy-efficient homes allow poorer air exchange, increases in adverse drug effects, and changes in availability and use of health care (Tepper et al., 1986; Martinez et al., 1988). Increases in day care use with subsequent increases in exposure to viral infections, maternal smoking rate and a larger cohort of low birth weight infants surviving with subsequent increased risk of obstructive lung diseases are also factors (Chan et al., 1989).

Our study included 100 known-asthmatic Egyptian children selected from the Pediatrics Department (outpatient and inpatient) of Al Matariah Teaching Hospital – Cairo. Their ages ranged from 7 to 15 years with a mean of 9.9 (years) ± 2.1 S.D., they were divided into 3 distinct groups of different severities of asthma (according to the criteria of the Guidelines for the Diagnosis and Management of Asthma, 1991):
mild, moderate and severe. They were selected in the study so as to have an equal number of both sexes.

The study showed that there is a female preponderance in the mild asthma group (n= 33) with a female: male ratio of 1.75:1, in contrast to a male preponderance in the severe asthma group (n= 38) with a male: female ratio of 1.53:1. In the moderate asthma group (n= 29) the female to male ratio is almost 1:1. These findings show that asthma was more severe among males than females in the studied asthmatic patients of that age group.
This correlates with the statement that asthma tends to be more severe in young boys than girls (Williams, McNichol, 1969; Dodge, Burrows, 1980).

This gender difference in relation to the severity of asthma was not equally pronounced in relation to the presence of sinusitis among our studied group of patients. The total number of male patients which were suffering from sinusitis was 17 while the total number of female patients with sinusitis was 14 with a male: female ratio of 1.2:1.

The age of the onset of wheezing in the studied patients had a statistically significant correlation with the degree of severity of asthma being younger in the mild asthma group (n= 33) with a mean of 4.1 (years) ± 3.2 S.D. than in the other two groups

where there are a mean of 5.8 (years) ± 2.4 S.D. in the moderate asthma group (n= 29) and a mean of 5.7 (years) ± 2.6 S.D. in the severe asthma group (n= 38).
This shows that asthma had a tendency to be milder among the studied patients who started to wheeze early.
This has some agreement with the literature as one study found that wheezing that began after age 2 was associated with a greater persistence of wheezing at age 11, as compared with wheezing that began before age 2 (Sporik et al., 1991). Though in a study conducted on 120 asthmatic Egyptian children, there was no statistically significant difference between age of the onset and the severity of the disease (El Heneidy et al., 1989).

On the other hand, the age of the onset of wheezing in our studied patients had no statistically significant correlation with the presence of sinusitis among them, the results showed a mean of 5.2 (years) ± 2.8 S.D. in those patients without sinusitis (n= 69) and a mean of 5.2 (years) ± 2.9 S.D. in those patients suffering from sinusitis.

A positive family history of allergy was found in 27% of the total number of the patients. Although, there was no statistically significant correlation between the positive family history of allergy and the degree of severity of asthma in our studied group, yet, the percentage of positive family history of allergy is highest in the severe asthma group being 34.2%, followed by 31 % in the moderate asthma group while it is only 15.2% in the mild asthma group. This is in agreement with the finding of 39% of positive family history of allergy among Egyptian asthmatic children with lack of statistically significant correlation between the positive family history of allergy and the degree of asthma severity (El Heneidy et al., 1989). This finding is also in

agreement with what Sly stated in 1996 that the atopic allergy tend to be familial, asthma may be familial whether or not it is due to allergy and that nonetheless, asthma can also occur without a positive family history.

A statistically significant correlation between a positive family history of allergy and the presence of sinusitis was noted, as it was positive in 48.4% of patients suffering from sinusitis (n= 31) while it was only positive in 17.4% of patients free from sinusitis (n= 69), this is in agreement with the report of Richards et al. (1991) of a significant family history of atopy among children suffering from chronic sinusitis (approximately 77% of cases).

No statisticallly significant correlation was found between parental smoking and the severity of asthma nor the presence of sinusitis.
Parental smoking was found in 28% of the total number of patients with a distribution as follows: 23.7% (n= 38) among severe asthma group, 34.5% (n= 29) among moderate asthma group and 27.3% (n= 33) among mild asthma group.
Although parental, particularly maternal, smoking has been clearly associated with an increased risk of wheezing, respiratory symptoms, lower respiratory tract illness, and hospitalization in exposed infants (Coley et al.; 1974; Harlap, Davies, 1974; Ware et al., 1984; Wright et al., 1991). In a study of 1246 children followed from birth, Wright et al. (1991) demonstrated that infants exposed to mothers who smoked at least one pack of cigarettes per day had 2.8 times the risk of developing a lower respiratory tract illness. Infants exposed to this level of maternal smoking also developed these illnesses an average of 1.5 months earlier in life. The effect of maternal smoking has been assumed

to be due to passive inhalation of sidestream tobacco smoke by the infant. This might then result in airway inflammation and other alterations favoring both viral infection and the development of clinical wheezing illness or pneumonia. Preliminary results from several studies have suggested that this relationship also may be due to alteration of the developing lung by maternal smoking, (Hanrahan et al., 1990; Neddenriep et al.; 1990) leading to a greater risk for wheeze with infection. Maternal smoking during pregnancy results in fetal stress secondary to both intrauterine hypoxia and nicotine exposure. Whereas the growth retardation associated with maternal smoking during pregnancy is well known, lung-specific effects may occur as well as, including a reduction in lung elastin content (Collins et al., 1985). Even passive cigarette smoke exposure increases the incidence of asthma flare-ups and emergency room visits. The effect is more pronounced in atopic children. Though exposure to smoke does not appear to be an independent trigger responsible for an acute exacerbation of asthma, the adverse outcomes on poor control of chronic asthma are dose-related to the amount of exposure (Fischer et al., 1995). The lack of statistical correlation between parental smoking and the degree of severity of asthma can be attributed to the increasing public awareness of the hazards of passive smoking, especially for children and in particular the chesty ones, and that might be a cause of parental refrain from smoking in the vicinity of their children.

Presence of pets in the environment was found in 21% of the total number of the patients and is distributed as follows: 13.2% (n= 38) in the severe asthma group, 24.1% (n= 29) in the moderate asthma group and 27.3% in the mild asthma group, which means that there is no statistically significant difference

among the three groups regarding the presence of pets. A finding which can be explained by pets elimination from the direct patient's environment as part of the general guidelines of treatment of asthma, because a pet in the home can be a major source of allergen. Animals can spread not only their own allergens but also dust mite, pollens and molds that adhere to the coat. The most effective way to decrease animal allergen in the home is to remove the pet completely (Woods et al., 1989).

Also, there was no significant statistical correlation between the presence of pets and the prevalence of sinusitis among the patients.

There was a history of positive food allergy in 16% of the total number of patients: 15.8% (n= 38) in the severe asthma group, 13.8% (n= 29) in the moderate asthma group and 18.2% (n= 33) in the mild asthma group. There was no significant statistical correlation between the severity of asthma and the presence of food allergy. The same applies to the presence of sinusitis, only 9.7% of those with sinusitis had a positive history of food allergy (n= 31). This is in agreement with what November et al. (1988) had stated that "food allergy is frequently invoked to explain asthma, in reality this is not often the case". November et al. (1988) conducted a study using history, skin tests, radioallergosorbent test, and double blind food challenge, they found asthma related to food allergy in only 8 of 140 patients. This is because wheezing may be a manifestation of food allergy but is rarely the sole symptom. Wheezing, when it occurs from food hypersensitivity is ususally accompanied by gastro-intestinal or cutaneous symptoms such as nausea, vomiting, urticaria and angioedema (Reid, 1992).

Allergy to insect bites was found in 22% of the total number of patients: 21.0% (n= 38) in severe asthma group, 20.7% in moderate asthma group and 24.2% in mild asthma group, that means that the presence of allergy to insect bites is not statistically correlated with the degree of severity of asthma among the studied patients.

The same applies to the presence of sinusitis among them, only 25.8% (n= 38) of those with sinusitis had a positive history of allergy to insect bites.

Reaction to drugs was reported in 14% of the total number of patients and was distributed as follows: 10.5% (n= 38) in the severe asthma group, 20.7% (n= 29) in the moderate asthma group and 12.1% in the mild asthma group (n= 33), that means that there was no statistically significant correlation between the positive history of a drug reaction and the degree of severity of asthma in the studied patients.

The same was found in relation to the presence of sinusitis in the patients as drug reaction was only reported in 19.4% of patients suffering from sinusitis (n= 31) which was not statistically significant.

This is in agreement with the literature as the well known aspirin-induced asthma has an incidence of 13% to 19% on oral challenge techniques in both children and adults (Settipane et al., 1972; Shatz et al., 1988).

Allergic conjunctivitis was reported in 17% of the total number of patients: 23.7% (n= 38) in the severe asthma group, 13.8% (n= 29) in the moderate asthma group and 12.1% (n= 33) in the mild asthma group. There was no statistically significant difference among the three groups. Also, there was no

statistically significant correlation between allergic conjunctivitis and the presence of sinusitis 25.8% (n= 31).

Skin atopic manifestations were found in 46% of the total number of patients which is exactly in agreement with a report of 46% prevalence of atopic eczema among boys and girls with asthma in the north east of England (Shamssain, Shamsian, 1999). Although a correlation between the presence of atopic dermatitis and the severity of asthma, or the presence of sinusitis could not be proved by the results.

The study showed a statistically significant decrease in the PEFR that is correlating with the degree of severity of asthma, being more pronounced in the severe group.

Also, there is a statistically significant ascending gradient in the amount of elevation of eosinophil number in the blood and the total serum IgE level from the mild asthma group (n= 33) to the moderate asthma (n= 29)group to the severe asthma group (n= 38).The same finding was noted with the presence of sinusitis as the eosinophil count and total serum IgE level had a statistically significant elevation in the patients suffering from sinusitis than in patients free of sinusitis.

The radiological findings of the chest and of the sinuses were statistically significant with the degree of severity of asthma in the studied group of patients.
Relevant chest x-ray findings were reported in 36% of the total number of cases: 52.6% (n= 38) in the severe asthma group, 34.5 % (n= 29) in the moderate asthma group and 18.2% (n= 33) in the mild asthma group which means that the positive chest x-ray findings had a statistically significant correlation with the degree

of severity of asthma in the studied patients which is in agreement with the literature (Ellis, 1988; Lawlor, Tashkin, 1995). The same finding was noted in relation to the presence of sinusitis: 61.3% of cases that had sinusitis (n= 31) had relevant chest x-ray findings which is statistically significant.
Radiological evidence of sinusitis occurred in 34% of the total number of patients, this percentage approaches the percentage published in some previous studies. Overall it has been established that 40% to 50% of both adults and children with asthma have abnormal sinus radiographs (Weille, 1936; Businco et al., 1981; Slavin, 1982). The distribution of the positive radiogrophic findings of sinusitis among the studied patients was as follows: 52.6% (n= 38) in the severe asthma group, 27.6% (n= 29) in the moderate asthma group and 18.2% in the mild asthma group which constitutes a statistically significant correlation between the radiological evidence of sinusitis and the degree of asthma severity in the studied cases.
Again, radiological evidence of sinusitis was highly significant statistically with cases of clinically diagnosed sinusitis 96.8% (n= 31).This is in agreement with the literature (Kuhn; 1986; Ellis, 1988), also Richards et al. (1991) reported positive radiological evidences for sinusitis in 91.6% of clinically diagnosed sinusitis in children.

Inhalant skin sensitivity testing was positive in 42% of the total number of patients and distributed as follows: 52.6% (n= 38) in the severe asthma group, 34.5% (n= 29) in the moderate asthma group and 36.4% (n= 33) in the mild asthma group which means that there is no significant statistical correlation between the skin test positivity and the degree of asthma severity. This is in agreement with the results reported by Abdel Fatah (1996) who found a 49% positive skin test recativity among a group of

Egyptian asthmatic children with no relation between the skin test positivity and the degree of asthma severity.

In contrast, prevalence of positive skin test was highly significant statistically in the studied patients who had sinusitis: 71.0% (n= 31). Nguyen et al. (1993) reported a prevalence of positive skin test reactivity in 63% of their studied children suffering from chronic sinusitis and chronic respiratory complaints (n= 51).

It is worthnoted that the most commonly positive inhalant allergen in the skin test among the reacting patients was the house dust mix (69%) followed by the Aspergillus mix (28.5%) then the Penicillium mix (26%). Again, this goes hand in hand with the findings reported in the literature (El Heneidi et al., 1989; Sultan et al., 1992).

Allergic rhinitis was found in 37% of the total number of patients which is in agreement with the finding that 28% to 61% of asthmatic patients may have associated allergic rhinitis (Blair, 1977; Barbee et al., 1987). A most recent study reports that allergic rhinitis was found in 44% and 40% of boys and girls with asthma, respectively, in the north east of England (Shamssain M.H., Shamsian N., 1999).

Again, a statistically significant prevalence of allergic rhinitis was found in the more severe asthma group than in the other two groups, as follows: allergic rhinitis was found in 55.3% (n= 38) of the patients with severe asthma, 34.5% (n= 29) of the patients with moderate asthma and 18.2% (n= 33) of the patients with mild asthma. This in agreement with the finding that allergic rhinitis is significantly greater in the more severe asthmatic patients than in the less severe asthmatic patients or controls (Kelly et al., 1987).

Also, the study showed a statistically significant prevalence of sinusitis among those asthmatic patients with allergic rhinitis amounting to 87.1% (n= 37). These findings are explained by the concept that allergic rhinitis, a symptom complex resulting from exposure to a specific antigen, can result in complications such as sinusitis, recurrent ear infections, or nasal polyps. The important allergens in allergic rhinitis are usually airborne substances to which atopic patient has become sensitized (e.g. pollens, dust mites and animal dandres). The pathophysiology of allergic rhinitis is quite similar to what happens in extrinsic asthma: sensitization of allergic persons follows inhalation of antigen. On reexposure, soluble antigens pass through the nasal mucosa to react with IgE fixed to mast cells. Mast cell degranulation results in release of mediators such as histamine, leukotrienes, prostaglandins and kinins. These mediators induce vasodilation and increased vascular permeability, resulting in mucosal edema, increased mucus production, and symptoms of nasal itching and sneezing. Chemotactic factors are also released and lead to an influx primarily of eosinophils, as well as neutrophils, mononuclear cells, and basophils. There is evidence that the eosinophils are activated, releasing major basic protein and other toxic mediators which can cause extensive mucosal injury (Lawlor, Tashkin, 1995).

The results showed that 31% of the total number of patients had sinusitis (acute or chronic) as evidenced by the clinical findings at the time of inclusion in the study. Although the result is not statistically significant, yet this percentage approaches the percentage published in some previous studies as Nguyen et al. (1993) reported a 34.7% prevalence of sinusitis among a group of asthmatic American children.

However, on analyzing findings of the cases that were suffering from sinusitis we found that 54.8% of them had severe asthma, while 25.8% of them had moderate asthma and that 19.4 % of them had mild asthma (n= 31) which is statistically significant. This can be explained by the concept that the principal pathogenic mechanism of most pediatric asthma involves antigen-triggered respiratory mucosal inflammation (McFadden, Gilbert, 1992), the role of the nose in filtering air takes on added significance (Druce, Slavin, 1991; Kaliner, Lemanske, 1992) and the impaired mucociliary clearance during acute or chronic sinusitis may exacerbate asthma by increasing the antigen load to bronchial mucosa (Manning et al., 1994).

On summing up the previously-mentioned results, the following is noticed:
Sinusitis was prevalent in almost the third of the studied asthmatic children irrespective of gender type or age of the onset of wheezing.

The sinusitis was more prevalent in the severe asthmatics than in the patients who had a milder form of asthma, also, sinusitis was found more in patients having a positive family history of asthma, in those with allergic rhinitis, in those with positive skin test reactivity, in those with higher eosinophil count and in those with higher total serum IgE level.

This means that sinusitis tended to occur more commonly in the severe allergic (extrinsic) asthma than in the milder non-allergic (intrinsic) asthma among the studied group of Egyptian asthmatic children.

This is in agreement with the idea that the presence of sinusitis is considered an association of severe allergic childhood asthma and is an aggravating factor of asthma in children.

SUMMARY
AND
CONCLUSION

Bronchial asthma is a major health hazard in childhood. It is the most frequent admitting disease in children's hospitals. Asthma may be regarded as a diffuse obstructive lung disease with 1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment; 2) airway inflammation; and 3) increased responsiveness to a variety of stimuli. In some patients with so-called extrinsic or allergic asthma, attacks follow exposure to environmental factors such as dust, pollens and danders. Often but not always, such patients have increased concentrations both of total IgE and of specific IgE against the antigen implicated. In other patients with clinically similar asthma, there is no evidence of IgE involvement, skin tests are negative and IgE concentrations low. This form of asthma has been called intrinsic (Sly, 1996).

Different works had studied the presence of a relationship between sinusitis and asthmatic children, in the belief that there is a higher incidence of sinusitis among asthmatic children more than in normal children and that the severity of the asthma is increased in presence of sinusitis. Some other studies doubt these findings.

In this study, 100 known-asthmatic Egyptian children (50 boys and 50 girls) had been selected from the Pediatrics Department (outpatient and inpatient) of Al Matariah Teaching Hospital – Cairo during the period from the beginning of January 1995 till the end of April 1996. Their ages ranged from 7 to 15 years with a mean of 9.9 years $\pm$ 2.1 S.D..

They had all been subjected to the following:
- Full medical and allergic history taking.
- Complete clinical examination.
- P.E.F.R. recording (twice for every patient: without treatment

and under treatment control).
- Skin sensitivity test (prick method).
- Total serum IgE determination by E.L.I.S.A. method.
- Complete blood count.
- Chest x-ray.
- X-ray of paranasal sinuses.

On analyzing the data and the results of the study, the selected patients were divided into three groups according to the degree of severity of their asthma as follows:
A group of mild asthma (33 patients), a group of moderate asthma (29 patients) and a group of severe asthma (38 patients).

The results of the study showed the following:

- There is a significant statistical evidence that the age of the onset of asthma was younger in the mild asthma group in comparison with the other two groups (moderate and severe).
- There is an ascending gradient in the percentage of decrease of the P.E.F.R. from the mild asthma group to the moderate asthma group to the severe asthma group.
- The group of severe asthma had a statistically significant higher prevalence of allergic rhinitis, presence of positive chest x-ray findings and radiological evidences of sinusitis.
- There is an ascending gradient in the amount of increase of the eosinophilic count (%) in the blood and the total serum IgE level from the mild asthma group to the moderate asthma group to the severe asthma group.

The results also showed that 31% of the studied patients were suffering from sinusitis, that is a percentage which approaches some of the figures in the studies done abroad, also it has been

found that among these patients the prevalence of severe asthma was 54.8% which is statistically significant.

In addition, there has been observed significant statistical evidences between the presence of sinusitis and a positive family history of allergy, presence of allergic rhinitis, skin test positivity, a more marked eosinophilia in the blood and a higher level of total serum IgE.

In conclusion, this study has proved a relationship between the presence of sinusitis and the degree of severity of asthma among the studied Egyptian asthmatic children, being more prevalent in the severe form of asthma. It has also proved the more frequent association of extrinsic (allergic) type of asthma than the intrinsic (non-allergic) type with the sinusitis among the studied group of asthmatic patients.

This is in agreement with the concept that sinusitis is considered an association of severe asthma and one of its aggravating factors and that sinusitis in such cases should be actively managed.

RECOMMENDATIONS

According to the results of this study, it is recommended that all pediatric patients suffering from severe asthma, especially those who are refractory to treatment, be subjected to a thorough search for the presence of sinusitis. They should be clinically examined for sinusitis, have a radiological examination of their sinuses whether by plain x-ray or C.T. scanning, and they should also have Fibre-optic endoscopic examination if required.

This is in particular in the severe asthmatic children showing the following criteria:

- Family history of allergy.
- Signs of allergic rhinitis.
- Positive skin sensitivity test results, especially to house dust mix.
- Chest x-ray abnormalities.
- Elevated eosinophilic count.
- Elevated Total Serum IgE level.

It is also recommended to actively manage and treat the sinusitis, once diagnosed, in asthmatic patients in order to get a better control of their pulmonary symptoms.

REFERENCES

Aas K. (1971):
Controlled trial of hyposensitization to house dust
Acta Paediatrica Scand.; 60: 264-268.

Abdel Fatah A. (1996):
Study of antigenic profile of asthmatic children in Alexandria.
M.D. Thesis, Pediatrics. Faculty of Medicine. University of Alexandria (Egypt).

Abou El Magd A., Atwa S. and Abou El Fadel M. (1991):
Effect of nutritional status on some immunological aspects in asthmatic children.
Proc. 9th. Ann. Sci. Conf. of Faculty of Medicine, Assiut University: pp.131-136.

Adinoff A.D., Cummings N.P. (1989):
Sinusitis and its relationship to asthma.
Pediatr. Ann.; 18: 785-790.

Agertoft L. Pedersen S. (1994):
Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children.
Respir. Med.; 88: 373-381.

Allen D.B. (1996):
Growth suppression by glucocorticoid therapy. In:
Vassallo J. (ed.). Endocrinology and Metabolism Clinics in North America. Philadelphia: W.B. Saunders Co.; pp. 699-717.

Allen D.B., Lemanske R.F. Jr. (1993):
The safety of chronic asthma treatments: continuous beta - agonist therapy and prolonged inhaled corticosteroids in childhood asthma. In:
Middleton E. Jr., Reed C.E., Ellis E.F., Adkinson N.F. Jr., Yunginger J.W., Busse W.W. (eds.). Allergy: Principles and Practice. 4th. ed. St. Louis, M.O.: Mosby Yearbook; pp. 1-16.

Allen D.B., Mullen M., Mullen B. (1994):
A meta-analysis of the effect of oral and inhaled corticosteroids on growth.

J. Allergy Clin. Immunol.; 93: 967-976.

Allen D.H., Delohery J., Baker G. (1987):
Monosodium L- glutamate- induced asthma.
J. Allergy Clin. Immunol.; 80: 530-537.

Allphin A.L., Strauss M., Abdul-Karim F.W. (1991):
Allergic fungal sinusitis: problems in diagnosis and treatment.
Laryngoscope; 101: 815-820.

Alton E., Norris A.A. (1996):
Chloride transport and the actions of nedocromil sodium and cromolyn sodium in asthma.
J. Allergy Clin. Immunol.; 98: S102-106.

American Academy of Pediatrics Committee on Infectious Diseases (1995):
Recommendations for the use of live attenuated varicella vaccine.
Pediatrics; 5: 791-796.

American Thoracic Society (1991):
Lung function testing: Selection of reference values and interpretive strategies.
Am. Rev. Respir. Dis., 144: 1202-1218.

Anderson H.R., Pottier A.C., Strachan D.P. (1992):
Asthma from birth to age 23: Incidence and relation to prior and concurrent atopic disease.
Thorax; 47: 547-542.

Anderson S.D. (1988):
Exercise-induced asthma. In:
Middleton E., Reed C.E., Ellis E.F. et al. (eds.). Allergy Principles and Practice. 3rd. ed. St. Louis, Mosby, pp. 1343-1367.

Atef A., Khatab M., Sobhy A., El Baz H. (1995):
Study of the prevalence of bronchial asthma and related risk factors in primary school children in El Salam area in Port-Said.
The New Egyptian Journal of Medicine; vol. 12 (1): 121-125.

Aust R., Drettner B. (1974):
Oxygen tension in the human maxillary sinus under normal and pathological conditions.
Acta Otolaryngol.; 78: 264.

Awadh M.F. (1989):
Epidemiological study of the incidence of bronchial asthma among school children between 6-12 years in Tanta.
M. Sc. Thesis; Pediatrics. Faculty of Medicine. Cairo University (Egypt).

Axelsson A., Chidekel N. (1972):
Symptomatology and bacteriology of related to radiologic findings in acute maxillary sinusitis.
Acta Otolaryngol.; 74: 118.

Backer V., Groth S., Dirksen A, Bach-Mortensen N., Hansen K.K., Laursen E.M., Wendelboe D. (1991):
Sensitivity and specificity of the histamine challenge test for the diagnosis of asthma in an unselected sample of children and adolescents.
Eur. Respir. J.; 4: 1093-1100.

Badr El Din M.H., El Khattib M.A. (1999):
Chronic rhinosinusitis: treatment implications on childhood asthma.
The Medical Journal of Cairo University; vol. 67 (3): 189-193.

Balfour-Lynn L. (1986):
Growth and childhood asthma.
Arch. Dis. Child.; 61 (11): 1049-1055.

Bamberger D.M. (1991):
Antimicrobial treatment of sinusitis.
Semin. Respir. Infect.; 6 (2): 77-84.

Barbee R.A., Dodge R., Lebowitz M.L., Burrows B. (1985):
The epidemiology of asthma.
Chest; 87: 21S-25S.

Barbee R.A., Halonen M., Lebowitz M., Burrows B. (1981):
Distribution of IgE in a community population sample: correlations with age, sex and allergen skin test reactivity.
J. Allergy Clin. Immunol.; 68: 106-111.

Barbee R.A., Kalterborn W., Lebowitz M.D., Burrows B. (1987):
Longitudinal changes in allergen skin test reactivity in a community population sample.
J. Allergy Clin. Immunol.; 79: 16-24.

Bardana E.J. (1992):
What characterizes allergic asthma?
Ann. Allergy; 68: 371-373.

Bardin P.G., Johnston S.L., Pattemore P.K. (1992):
Viruses as precipitants of asthma symptoms. II. Physiology and mechanisms.
Clin. Exp. Allergy; 22: 809-822.

Bardin P.G., Van Heerden B.B., Joubent J.R. (1990):
Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis.
J. Allergy Clin. Immunol.; 86: 82-88.

Barnes P.J. (1992):
Neurogenic inflammation and asthma.
J. Asthma; 29: 165-180.

Barnes P.J. (1995):
Inhaled glucocorticoids for asthma.
N. Engl. J. Med.; 332: 868-875.

Barnes P.J., Baraniuk J.N., Belvis M.G. (1991):
Neuropeptides in the respiratory tract.
Am. Rev. Respir. Dis.; 144: 1187-1198.

Barnes P.J., Pedersen S. (1991):
Efficacy and safety of inhaled corticosteroids in asthma.
Am. Rev. Respir. Dis.; 148: S1-S26.

Barnes P.J., Thomson C. (1988):
Drug-induced asthma. In:
Barnes P.J., Rodger J.W., Thomson N.C. (eds.): Asthma Basic Mechanisms and Clinical Management. London, Academic Press; pp. 533-549.

Barros M.J., Rees P.J. (1990):
Bronchodilator responses to salbutamol followed by ipratropium bromide in partially reversible airflow obstruction.
Respir. Med.; 84: 371-375.

Beer S.I., Kannai Y.I., Waron M.J. (1991):
Acute exacerbation of bronchial asthma in children associated with afternoon weather changes.
Am. Rev. Respir. Dis.; 144: 31-35.

Bellia V., Visconti A., Insalaco G., Cuttita G., Ferrara G., Bonsignore G. (1988):
Validation of morning dip of peak expiratory flow as an indicator of the severity of nocturnal asthma.
Chest; 94: 108-110.

Bentley A.M., Menz G., Storz C., Robinson D.S., Bradley B., Jeffery P.K., Durham S.R., Kay A.B. (1992):
Identification of T lymphocytes, macrophages and activated eosinophils in the bronchial mucosa in intrinsic asthma. Relationship to symptoms and bronchial hyper-responsiveness.
Am. Rev. Respir. Dis.; 146: 500-506.

Berg T., Johanson S.G. (1969):
Immunoglobulin levels during childhood, with special regard to IgE.
Acta Paediatr. Scand.; 58 (5): 513-524.

Bernstein I.L., Bernstein D.I., Dubb J.W., Faferman I., Wallin B. and participants of the Auranofin Multicenter Drug Trial (1996):
A placebo-controlled multicentre study of auranofin in the treatment of patients with corticosteroid-dependent asthma.
J. Allergy Clin. Immunol.; 98: 317-324.

Berquist W.E., Rachelefsky G.S., Kadden M., Siegel S.C., Katz R.M., Fonkalsrud E.W., Ament M.E. (1981):
Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children.
Pediatrics; 68: 29-35.

Bertelsen A., Andersen J.B., Busch P., Daugbjerg P., Friis B., Hansen L., Jacobsen S.V., Pelck I., Petersen W., Prahl P. et al. (1986):
Nebulized sodium cromoglycate in the treatment of wheezy bronchitis: a multicentre double-blind placebo controlled study.
Allergy, 41: 266-270.

Bierman C.W., Pearlman D.S. (1990):
Asthma. In: Chernick V., Kendig Jr. El. (eds.): Kendig's Disorders of the Respiratory Tract in Children. 5th ed. Philadelphia, W.B. Saunders, pp. 557-601.

Bisgaard H, Munck S.L., Nielsen J.P., Pedersen W., Ohlsson S.V. (1990):
Inhaled budesonide for treatment of recurrent wheezing in early childhood.
Lancet; 336: 649-651.

Bjornsdottir U.S., Busse W.W. (1992):
Respiratory infections and asthma.
Med. Clin. North. Am.; 76: 895-915.

Blair H. (1977):
Natural history of childhood asthma.
Arch. Dis. Child.; 52: 613-619.

Blanton P.L., Biggs N.L. (1969):
Eighteen hundred years of controversy: The paranasal sinuses.
Am. J. Anat.; 124: 135-147.

Bleecker E.R. (1985):
Airways reactivity and asthma: Significance and treatment.
J. Allergy Clin. Immunol.; 75: 21-24.

Boorsma M., Andersson N., Larsson P., Ullman A. (1996):
Assessment of the relative systemic potency of inhaled fluticasone and budesonide.
Eur. Respir. J.; 9: 1427-1432.

Booth H., Richmond I., Ward C., Gardiner P.V., Harkawat R., Walters E.H. (1995):
Effect of high dose inhaled fluticasone proprionate on airway inflammation in asthma.
Am. J. Respir. Crit. Care Med., 152: 45-52.

Bousquet J., Chanez P., Lacoste J.Y., Barneon G., Ghavanian N., Enander I., Venge P., Ahlstedt S., Simong-Lafontaine J., Godard P. et al. (1990):
Eosinophilic inflammation in asthma.
N. Engl. J. Med.; 323: 1033-1039.

Bousquet J., Hejjaoui A, Michel F-B (1990):
Specific immunotherapy in asthma.
J. Allergy Clin. Immnol.; 86: 292-305.

Bradley B.L., Azzawi M., Jacobson M, Assoufi B., Collins J.V., Irani A.M., Schwartz L.B., Durham S.R., Jeffery P.K., Kay A.B. (1991):
Eosinophils, T lymphocytes, mast cells, neutrophils and macrophages in bronchial biopsy specimens from atopic subjects with asthma: Comparison with biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyperresponsiveness.
J. Allergy Clin. Immunol.; 88: 661-674.

Britton J.R., Burney P.G., Chinn S., Papacosta A.O., Tattersfield A.E. (1988):
The relation between change in airway reactivity and change in respiratory symptoms and medication in a community survey.
Am. Rev. Respir. Dis.; 138: 530-534.

Britton J.R., Mortagy A., Tattersfield A.E. (1986):
Histamine challenge testing: Comparison of three methods.

Thorax; 41: 128-132.

Broder I., Higgins M.W., Mathews K.P., Keller J.B. (1974):
Epidemiology of asthma and allergic rhinitis in a total community. Tecumseh, Michigan. IV. Natural history.
J. Allergy Clin. Immunol.; 54: 100-110.

Brook I. (1971):
Aerobic and anaerobic bacterial flora of normal maxillary sinuses.
Laryngoscope; 92: 372.

Brook I. (1981):
Bacteriologic features of chronic sinusitis in children.
JAMA; 246: 967-969.

Brook I. (1989):
Bacteriology of chronic maxillary sinusitis in adults.
Ann. Otol. Rhinol. Laryngol.; 98: 426-428.

Brook I. (1992):
Diagnosis and management of anaerobic infections of the head and neck.
Ann. Otol. Rhinol. Laryngol.; 101: 9-13.

Brook I., Thompson D.H., Frazier E.H. (1994):
Microbiology and management of chronic maxillary sinusitis.
Arch. Otolaryngol. Head Neck Surg.; 120 (12): 1317-1320.

Brook I., Yocum P., Frazier E.H. (1996):
Bacteriology and beta-lactamase activity in acute and chronic maxillary sinusitis.
Arch. Otolaryngol. Head Neck Surg.; 122 (4): 418-422.

Brooks S.M., Weiss M.A., Bernstein I.L. (1985):
Reactive airways dysfunction syndrome (RADS): Persistent asthma syndrome after high-level irritant exposures.
Chest; 88: 376-384.

Brush J., Mathe A. (1993):

Psychiatric aspects. In:
Weiss E.B., Stein M., eds. Bronchial Asthma. Boston : Little, Brown and company; pp. 1121-1131.

Buffum W.P., Settipane G.A. (1966):
Prognosis of asthma in childhood.
Am. J. Dis. Child.; 112: 214-217.

Buist S.A., Vollmer WM (1990):
Reflections on the rise in asthma morbidity and mortality.
JAMA; 264: 1719-1720.

Bullen S.S. (1932):
The incidence of asthma in 400 cases of chronic sinusitis.
J. Allergy; 4: 402.

Burdon J.G.W., Juniper E.F., Killian K.J., Hargreave F.E., Campbell E.J. (1982):
The perception of breathlessness in asthma.
Am. Rev. Respir. Dis.; 126: 825-828.

Burr M.L., Butland B.K., King S., Vaughan-Williams E. (1989):
Changes in asthma prevalence: Two surveys 15 years apart.
Arch. Dis. Child.; 64 (10): 1452-1456.

Burrows B., Martinez F., Halonen, Barbee R.A., Cline M.G. (1989):
Association of asthma with serum IgE levels and skin-test reactivity to allergens.
N. Engl. J. Med.; 320: 271-277.

Bush A.K. (1992):
The role of allergens in asthma.
Chest: 101: 378S-380S.

Bush R.K., Taylor S.L. (1986):
A critical evaluation of clinical trials in reactions to sulfites.
J. Allergy Clin. Immunol.; 78: 191-202.

Businco L., Fiore L., Frediani T., Artuso A., Di Fazio A., Bellioni P. (1981):
Clinical and therapeutic aspects of sinusitis in children with bronchial asthma.
Int. J. Pediatr. Otorhinolaryngol.; 3 (4): 287-294.

Busse W.W. (1993):
What role for inhaled steroids in chronic asthma?
Chest; 104: 1565-1571.

Busse W.W., Kiecolt-Glaser J.K., Coe C., Martin R.J., Weiss S.T., Parker S.R. (1995):
NHLBI workshop summary. Stress and asthma.
Am. J. Respir. Crit. Care Med.; 151: 249-252.

Capewell S., Reynolds S., Shuttleworth D., Edwards C., Finlay A.Y. (1990):
Purpura and dermal thinning associated with high dose inhaled corticosteroids.
BMJ; 300: 1548-1551.

Carenfelt C., Eneroth C.M., Lundberg C., Wretland B (1975):
Evaluation of the antibiotic effect of treatment of maxillary sinusitis.
Scand. J. Infect. Dis.; 7: 259.

Carenfelt C., Lundberg C. (1976):
Aspects of the treatment of maxillary sinusitis.
Scand. J. Infect. Dis. Suppl.; 9: 78.

Carenfelt C., Lundberg C. (1977):
Purulent and non-purulent maxillary sinus secretions with respect to Po , Pco and pH.
Acta Otolaryngol.; 85: 116.

Casolaro V., Steve N.G., Zhimin S., Santa Jeremy O. (1996):
Biology and genetics of atopic disease.
Current opinion in Immunology; 8:796-803.

Chai H., Farr R.S., Froehlich L.A., Mathison D.A., Mclean J.A., Rosenthal R.R., Sheffer A.L., Spector S.L., Townley R.G. (1975):
Standardization of bronchial inhalation challenge procedures.
J. Allergy Clin. Immunol.; 56: 323-327.

Chan K.N., Noble-Jamieson C.M., Elliman A., Bryan E.M., Silverman M. (1989):
Lung function in children of low birth weight.
Arch. Dis. Child.; 64: 1284-1293.

Chapman K.R., Verbeek P.R., White J.G., Rebuck A.S. (1991):
Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma.
N. Engl. J. med.; 324: 788-794.

Chatham M., Bleecker E.R., Smith P.L., Rosenthal R.R., Mason P., Norman P.S. (1982):
A comparison of histamine, methacholine and exercise airway reactivity in normal and asthmatic subjects.
Am. Rev. Respir. Dis.; 126: 235-240.

Chobot R. (1930):
Incidence of sinusitis in asthmatic children.
Am. J. Dis. Child.; 137: 257.

Christopher K.L., Wood R.P., Eckert R.C., Blager F.B., Raney R.A., Souhrada J.F. (1983):
Vocal cord dysfunction presenting as asthma.
N. Engl. J. Med.; 308: 1566-1570.

CIBA Foundation Guest Symposium: Terminology, definitions, and classifications of chronic pulmonary emphysema and related conditions (1959):
Thorax; 14: 286-299.

Clark B. (1993):
General pharmacology, pharmacokinetics and toxicology of nedocromil sodium.
J. Allergy Clin. Immunol.; 92: 200-202.

Clark D.J., Grove a, Cargill R.I., Lipworth B.J. (1996):
Comparative adrenal suppression with inhaled budesonide and fluticasone proprionate in adult asthmatic patients.
Thorax; 51: 262-266.

Clark N.M., Evans D., Mellins R.B. (1992):
Pulmonary perspective: Patient use of peak flow monitoring.
Am. Rev. Respir. Dis.; 145: 722-725.

Clifford R.D., Radford M., Howell J.B., Holgate S.T. (1989):
Prevalence of respiratory symptoms among 7 and 11 year old school children and association with asthma.
Arch. Dis. Child.; 64: 1118-1125.

Clough B., William's J.D., Holgate S.T. (1991):
Effect of atopy on the natural history of symptoms, peak expiratory flow, and bronchial hyperresponsiveness in 7- and 8-year old children with cough and wheeze.
Am. Rev. Respir. Dis.; 143: 755-760.

Cloutier M.M., Loughlin G.M. (1981):
Chronic cough in children: A manifestation of airway hyperreactivity.
Pediatrics; 67: 6-12.

Cockcroft D.W. (1988):
Allergens. In:
Barnes P.B., Rodger I.W., Thomson N.C. (eds.): Asthma Basic Mechanisms and Clinical Management. London, Academic Press, pp. 455-464.

Cockcroft D.W., Berscheid B.A., Murdock K.Y. (1983):
Unimodal distribution of bronchial responsiveness to inhaled histamine in a random population.
Chest; 83: 751-754.

Cockcroft D.W., Berscheid B.A., Murdock K.Y. (1983):
Bronchial response to inhaled histamine in asymptomatic young smokers.

Eur. J. Respir. Dis.; 64: 207-211.

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

Cockroft D.W., McParland C.P., Britto S.A., Swystun Va., Rutherford B.C. (1993):
Regular inhaled salbutamol and airway responsiveness to allergen.
Lancet; 342: 833-837.

Cockroft D.W., Murdock K.Y. (1987):
Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone diproprionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine.
J. Allergy Clin. Immunol.; 79: 734-740.

Coley J., Holland W. and Corkhill R. (1974).
Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood.
Lancet 2: 1031.

Collins M., Moessinger A., Kleinerman J., Bassi J., Rosso P., Collins A.M., James L.S., Blanc W.A. (1985):
Fetal lung hypoplasia associated with maternal smoking: A morphometric analysis.
Pediatr. Res., 19: 408.

Connett G.J., Warde C., Wooter E., Lenney W. (1993):
Use of budesonide in severe asthmatics aged 1-3 years.
Arch. Dis. Child.; 69: 351-355.

Connett G.J., Warde C., Wooler E., Lenney W. (1994):
Prednisolone and salbutamol in the hospital treatment of acute asthma.
Arch. Dis. Child.; 70: 170-173.

Corey J.P. (1992):
Allergic fungal sinusitis.
Otolaryngol. Clin. North Am.; 25 (1): 225-230.

Corey J.P., Romberger C.F., Shaw G.Y. (1990):
Fungal diseases of the sinuses.
Otolaryngol. Head Neck Surg.; 103 (6): 1012-1015.

Corrao W.H., Brannen S.S., Irwin R.S. (1979):
Chronic cough as the sole presenting manifestation of bronchial asthma.
N. Engl. J. Med.; 300: 633-637.

Corrigan C.J., Kay A.B. (1990):
CD4+ T-lymphocyte activation in acute severe asthma. Relationship to disease severity and atopic status.
Am. Rev. Respir. Dis.; 141: 970-977.

Crater S.E., Platts-Mills T.A. (1998):
Searching for the cause of the increase in asthma.
Curr. Opin. Pediatr.; 10 (6): 594–599.

Creticos P, Burk J., Smith L., Comp R., Norman P., Findlay S. (1995):
The use of twice daily nedocromil sodium in the treatment of asthma.
J. Allergy Clin. Immunol.; 5: 829-836.

Croner S., Kjellman N.-I.M. (1992):
Natural history of bronchial asthma in childhood.
Allergy; 47: 150-157.

Cross D., Nelson H.S. (1991):
The role of the peak flow meter in the diagnosis and management of asthma.
J. Allergy Clin. Immunol.; 87: 120-128.

Cummings N.P., Wood R.W., Lere J.L., Adinoff A.D. (1983):

Effect of treatment of rhinitis/sinusitis on asthma: results of a double blind study.
Pediatr. Res.; 17: 373.

D' Allonzo G.E., Nathan R. A., Henochowicz S., Morris R. J., Ratner P., Rennard S. I. (1994):
Salmeterol xinafoate as maintenance therapy compared with asthma.
JAMA; 271: 1412-1416.

Daele J.J. (1997):
Chronic sinusitis in children.
Acta Otorhinolaryngol. Belg.; 51 (4): 285-304.

Dahlen B., Zetterstrom O., Ojorck T. Dahlen S. E. (1994):
The leukotriene-antagonist IC:204,219 inhibits the early airway reaction to cumulative bronchial challenge with allergen in atopic asthmatics.
Eur. Respir. J.; 7: 324-331.

Daley C.L., Sande M. (1988):
The runny nose: infection of the paranasal sinuses.
Infect. Dis. Clin. North Am.; 2: 131.

Davies R.S., Larsen G.L., Grunstein M.M.(1983):
Respiratory response to intraesophageal acid infusion in asthmatic children during sleep.
J. Allergy Clin. Immunol.; 72: 393-398.

Davison F.W. (1969):
Chronic sinusitis and infectious asthma.
Arch. Otolaryngol. Head Neck Surg.; 90:110.

deBenedictis F.M., Tuteri G., Pazzelli P., Bertotto A, Bruni L., Vaccaro R. (1995):
Cromolyn versus nedocromil: duration of action in exercise-induced asthma in children.
J. Allergy Clin. Immunol.; 96: 510-514.

DeBlay F., Chapman M.D., Platts-Mills T.A.E. (1991):

Airborne cat allergen (Fel d 1) environmental control with the cat in situ.
Am. Rev. Respir. Dis.; 143: 1334-1339.

Desreumaux P., Capron M. (1996):
Eosinophils in allergic reactions.
Current Opinion in Immunology; 8: 790-795.

Diament M.J. (1992):
The diagnosis of sinusitis in infants and children: X-ray, computed tomography and magnetic resonance imaging.
J. Allergy Clin. Immunol.; 90 (3): 442-444.

Dixon C.M.S., Barnes P.J. (1989):
Bradykinin-induced bronchoconstriction: inhibition by nedocromil sodium and sodium cromoglycate.
Br. J. Clin. Pharmcol.; 27: 831-836.

Dixon W., Massey F. (1983):
Introduction to Statistical Analysis. Fourth edition. McGraw-Hill.

Djukanovic R., Roche W.R., Wilson J.W., Beasley C.R., Twentyman O.P., howarth R.H., Holgate S.T. (1990):
Mucosal inflammation in asthma.
Am. Rev. Respir. Dis.; 142: 434-457.

Dodge R.R., Burrows B. (1980):
The prevalence of asthma and asthma-like symptoms in a general population sample.
Am. Rev. Respir. Dis.; 122: 567-575.

Doull I.J.M., Freezer N.J., Holgate S.T. (1995):
Growth of pre-pubertal children with mild asthma treated with inhaled beclomethasone diproprionate.
Am. J. Resp. Crit. Care Med.; 151: 1715-1719.

Dowse G.K., Turner K.J., Stewart G.A., Alpers M.P., Woolcock A.J., (1985):

The association between Dermatophagoides mites and the increasing prevalence of asthma in village communities within the Papua New Guinea highlands.
J. Allergy Clin. Immunol., 75: 75-83.

Drazen J.M., Israel E., Boushey H.A., Chinchilli V.M., Fahy J.V., Fish J.E., Lazarus S.C., Lemanske R.F., Martin R.J., Peters S.P., Sorkness C., Szefler S.J. (1996):
Comparison of regularly scheduled with as-needed use of albuterol in mild asthma.
N. Engl. J. Med.; 335: 841-847.

Drettner B., Aust R. (1977):
Pathophysiology of the paranasal sinuses.
Acta Otolaryngol.; 83: 16.

Druce H.M. (1990):
Adjuncts to medical management of sinusitis.
Otolaryngol. Head Neck Surg.; 103 (5): 880-883.

Druce H.M. (1992):
Diagnosis of sinusitis in adults: history, physical examination, nasal cytology, echo and rhinoscope.
J. Allergy Clin. Immunol.; 90 (3): 436-441.

Druce H.M., Slavin R.G. (1991):
Sinusitis and its relationship to asthma and allergy. In:
Schultz M., Zeiger R.S., Settipane G.A. Nasal Manifestations of systemic Diseases. Providence, R.I.: Oceanside Publisher Inc.; 35-47.

Dubois J., Saint-Pierre C., Tremblay C. (1993):
Efficacy of clarithromycin vs. amoxicillin/clavulonate in the treatment of acute maxillary sinusitis.
E.N.T. Journal; 72 (12): 804-810.

Dykewicz M.S. (1992):
Allergen immunotherapy for the patient with asthma.
Immunol. Allergy Clin. North Am.; 12: 125-143.

Eady R.P. (1986):
The pharmacology of nedocromil sodium.
Eur. J. Respir. Dis.; 147 (Suppl.): 112-119.

Eigen H., Laughlin J.J., Homrighausen J. (1982):
Recurrent pneumonia in children and its relationship to bronchial hyperreactivity.
Pediatrics; 70: 698-704.

El Hefny A., Nassar S., El Heneidy F., Said M., El Beleidy A., El Marsafy E., Mostafa N., El Falaky M., Haddad Z. (1994):
Epidemiology of Childhood Asthma in Cairo.
Med. J. Cairo Univ.; vol. 62 (2): 505-518.

El Heneidy F., El Hefny A., El Beleidy A. (1989):
Common inhalant allergens in extrinsic atopic asthmatic children in rural areas in Egypt.
Med. J. Cairo Univ.; vol. 57 (4): 897-904.

El Heneidy F., El Hefny A., Nassar S., El Beleidy A., Said M., El Falaky M., Mostafa N., Haddad Z. (1994):
A clinical study on asthmatic children in Cairo.
The Gaz. Egypt. Ped. Ass.; Vol. 42 (1-2): 73-86.

Ellis E.F. (1988):
Asthma in infancy and childhood. In:
Middleton E., Reed C.E., Ellis E.F. (eds.): Allergy Principles and Practice. St. Louis, Mosby, pp.1037-1062.

Eloy P., Bertrand B., Rombaux P. (1997):
Medical and surgical management of chronic sinusitis.
Acta Otorhinolaryngol. Belg.; 51 (4): 271-284.

Empey D.W., Laitinen L.A., Jacobs L., Gold W.M., Nadel J.A. (1976):
Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infections.
Am. Rev. Respir. Dis.; 113: 131-139.

Enarson D.A., Vedal S., Schultzer M., Dybuncio A., Chan-Yeung M. (1987):
Asthma, asthma-like symptoms, chronic bronchitis and the degree of bronchial hyperresponsiveness in epidemiological surveys.
Am. Rev. Respir. Dis.; 136: 613-617.

Eneroth C.M., Lundberg C. (1976):
The antibacterial effects of antibiotics in the treatment of maxillary sinusitis.
Acta Otolaryngol.; 81:475.

Engvall E. (1980):
Methods in Enzymology. VanVunatis H., Langone J.J. (eds.).
New York: Academic Press. Vol. 70: pp. 419-492.

Evans D., Levison M.J., Feldman C.H., Clark N.M., Wasilewski Y., Levin B, Mellins R.B. (1987):
The impact of passive smoking on emergency room visits of urban children with asthma.
Am. Rev. Respir. Dis.; 135: 567-572.

Evans F.O. Jr., Syndor J.B., Moore W.E. Moore G.R., Manwaring J.L., Brill A.H., Jackson R.T., Hanna S., Skaar J.S., Holdeman L.V. et al. (1975):
Sinusitis of the maxillary antrum.
N. Engl. J. Med.; 293:735.

Evans K.L. (1998):
Recognition and management of sinusitis.
Drugs; 56 (1): 59-71.

Evans R. III (1992):
Environmental control and immunotherapy for allergic disease.
J. Allergy Clin. Immunol.; 90 (3): 462-468.

Fanurik D., Hodgens B., Hanna D. (1991):
Hyperventilation syndrome in children and adolescents: A review with implications for research and practice.
Int. Pediatr.; 6: 269-275.

Fireman P. (1992):
Diagnosis of sinusitis in children: emphasis on the history and physical examination.
J. Allergy Clin. Immunol.; 90 (3): 433-436.

Fischer T.J., O'Brien K.P., Entis G.N. (1995):
Basic principles of therapy for allergic disease. In:
Lawlor G.J.Jr., Fischer T.J., Adelman D.C. (eds.).
Manual of Allergy and Immunology. Third edition. Little, Brown and Company, pp.: 51-93.

Frederick J., Braude A.L. (1974):
Anaerobic infection of the paranasal sinuses.
N. Engl. J. Med.; 290:135.

Friedman E.M., Coe C.L., Ershler W.B.(1994):
Bidirectional effects of interleukin-1 on immune responses in rhesus monkeys.
Brain Behav. Immun.; 8: 87-99.

Friedman R., Ackerman M., Wald E., Casselbrant M., Friday G., Fireman P. (1984):
Asthma and bacterial sinusitis in children.
J. Allergy Clin. Immunol.; 74: 185-189.

Fung K.P., Chow O.K., So S.Y. (1986):
Attenuation of exercise-induced asthma by acupuncture.
Lancet; 2: 1419-1422.

Gaddy J.N., Margolskee D.J., Bush R.K., Williams V.C., Busse W.W. (1992):
Bronchodilation with a potent and selective leukotriene D4 (LTD4) receptor antagonist (MK-571) in patients with asthma.
Am. Rev. Respir. Dis.; 146 (2): 358-363.

Galvez R.A., McLaughlin F.J., Levisin H. (1987):
The role of methacholine challenge in children with chronic cough.
J. Allergy Clin. Immunol.; 79: 331-335.

Gergen P.J., Mullaly D.I., Evans R. (1988):
National survey of prevalence of asthma among children in the United States, 1976- 1980.
Pediatrics; 81: 1-7.

Gergen P.J., Weiss K.B. (1990):
Changing patterns of asthma hospitalization among children: 1979-1987.
JAMA 1990; 264: 1688-1692.

Gergen P.J., Weiss K.B. (1992):
The increasing problem of asthma in the United States.
Am. Rev. Respir. Dis.; 146: 823-824.

Gerritsen J., Koeler G.H., deMonchy J.G.R., Knol K. (1990):
Allergy in subjects with asthma from childhood to adulthood.
J. Allergy Clin. Immunol.; 85: 116-125.

Gerritsen J., Koeler G.H., Postma D.S., Schouten J.P., Knol K. (1989):
Prognosis of asthma from childhood to adulthood.
Am. Rev. Respir. Dis.; 140: 1325-1330.

Gibbs C.J., Coutts II, Lock R., Finnegan O.C., White R.J. (1984):
Premenstrual exacerbation of asthma.
Thorax; 39: 833-836.

Gill F.F., Neiburger J.B. (1989):
The role of nasal cytology in the diagnosis of chronic sinusitis.
Am. J. Rhinol.; 3 (1): 13-15.

Gleich G.J. (1990):
The eosinophil and bronchial asthma: Current understanding.
J. Allergy Clin. Immunol.; 85: 422-435.

Godfrey S. (1985):
What is asthma.
Arch. Dis. Child.; 60: 997-1000.

Godfrey S. (1996):
Controversies in the pathogenesis of exercise-induced asthma.
Eur. J. Respir. Dis.; 68: 81-88.

Goldman J., Muers M. (1991):
Vocal cord dysfunction and wheezing.
Thorax; 46: 401-404.

Gonzalez J.P., Brogden R.N. (1987):
Nedocromil sodium. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of reversible obstructive airways disease.
Drugs; 34: 560-577.

Gottlieb M.J. (1925):
Relation of intranasal disease in the production of bronchial asthma.
JAMA; 85: 105-107.

Gourley D.S., Whisman B.A., Jorgensen N.L., Martin M.E., Reid M.J. (1990):
Allergic Bipolaris sinusitis: clinical immunopathologic characteritics.
Allergic Clin. Immunol.; 85: 583-591.

Grant E.N., Wagner R., Weiss K.B. (1999):
Observations on emerging patterns of asthma in our society.
J. Allergy Clin. Immunol.; 104 (2Pt 2): S1-9.

Grindlinger G.A., Niehoff J., Hughes L., Humphrey M.A., Simpson G. (1987):
Acute paranasal sinusitis related to nasotracheal intubation of head injured patients.
Crit. Care Med.; 15: 214-217.

Gross N.J., Petty T.L., Friedeman M., Skorodin M.S., Silvers G.W., Donohue J.F. (1989):
Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease.

Am. Rev. Respir. Dis.; 139: 1188-1191.

Guidelines for the diagnosis and management of asthma: National Heart, Lung, and Blood Institute, National Asthma Education Program Expert Panel Report (1991):
J. Allergy Clin. Immunol.; 88: 425-534.

Guidelines for the Diagnosis and Management of Asthma: National Heart, Lung, and Blood Institute, Clinical Practice Guidelines Expert Panel Report 2 (1997):
NIH Publication No. 97- 4051: 1-121.

Gwaltney J.M. (1979):
Sinusitis. In:
Benett M.D. (ed.). Principles and practice of infectious disease. New York: Wiley; 458.

Gwaltney J.M., Scheld W.M., Sande D.M., Sydnor (1992):
The microbial etiology and antimicrobial therapy of adults with acute community acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies.
J. Allergy Clin. Immunol.; 90 (3): 457-461.

Gwaltney J.M., Sydnor A., Sande M.A. (1981):
Etiology and antimicrobial treatment of acute sinusitis.
Ann. Otol. Rhinol. Laryngol. Suppl.; 90: 68-71.

Haahtela T., Jarvinen M., Kava T., Kiviranta K., Koskinen S., Lehtonen K., Nikander K., Persson T., Reinikainen K., Selroos O. et al. (1991):
Comparison of a beta 2-agonist, terbutaline, with inhaled corticosteroid, budesonide, in newly detected asthma.
N. Engl. J. Med.; 325: 388-392.

Hahn D.L., Dodge R.W., Galubjatnikov R. (1991):
Association of Chlamydia pneumoniae (strain TWAR) infection with wheezing, asthmatic bronchitis and adult-onset asthma.
JAMA; 266: 225-230.

Haahtela T., Jarvinen M., Kava T., Kiviranta K., Koskinen S., Lehtonen K., Nicander K., Persson T., Selroos O., Sovijarvi A. et al. (1994):
Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma.
N. Engl. J. Med.; 331: 700-705.

Haggag S. (1996):
Bronchial asthma prevalence among primary school children in Sharquia Governorate.
M.D. Thesis, Public Health. Faculty of Medicine. Zagazig University (Egypt).

Halken S., Host A., Husby S., Hansen L.G., Osterballe O., Nyboe J. (1991):
Recurrent wheezing in relation to environmental risk factors in infancy.
Allergy; 46: 507-514.

Hammerschlag M.R. (1992):
Is that pulmonary infection due to Chlamydia pneumoniae?
J. Respir. Dis.; 13:1385-1400.

Hanrahan J., Tager I., Segal M., Tosteson T., Castile R., Van Vunakis H., Weiss S., Speizer F. (1990):
Effect of prenatal smoking on infant lung function.
Am. Rev. Respir. Dis.; 141: A282.

Hargreave F.E., Dolovich J., O'Byrne P.M., Ramsdale E.H., Daniel E.E. (1986):
The origin of airway hyperresponsiveness.
J. Allergy Clin. Immunol.; 78: 825-832.

Hargreave F.E., Ryan G., Thomson N.C., O'Byrne P.M., Latimer K., Juniper E.F., Dolovich J. (1981):
Bronchial responsiveness to histamine or methacholine in asthma: Measurement and clinical significance.
J. Allergy Clin. Immunol.; 68: 347-355.

Harlap S., Davies A. (1974):

Infant admissions to hospital and maternal smoking.
Lancet 1: 529.

Harlin S.L., Ansel D.G., Lane S.R., Myers J., Kephart C.M., Gleich G.J. (1988):
A clinical and pathological study of chronic sinusitis.
J. Allergy Clin. Immunol.; 81: 867-875.

Harris J.B., Weinberger M.M., Nassif E., Smith G., Milavetz G., Stillerman A. (1987):
Early intervention with short courses of prednisolone to prevent progression of asthma in ambulatory patients incompletely responsive to bronchodilators.
J. Pediatr.; 110: 627-633.

Harrison A.C., Asher M.I., Pattemore P.K. (1986):
Do racial differences in asthma prevalence and severity account for racial differences in asthma admissions and mortality rates?
Am. Rev. Respir. Dis.; 133: A178.

Henderson W.R.Jr. (1994):
The role of leukotrienes in inflammation.
Ann. Intern. Med.; 121: 684-697.

Henderson W.R., Shelhamer J.H., Reingold D.B., Smith L.J., Evans R 3rd., Kaliner M. (1979):
Alpha-adrenergic hyperresponsiveness in asthma: Analysis of vascular and pupillary response.
N. Engl. J.Med.; 300: 642-646.

Herrera A.M., deShazo R.D. (1990):
Sinusitis. Its association with asthma.
Postgraduate Medicine; 87 (5): 153-156.

Herve P., Denjean A., Jian R., Simonneau G., Duraux P. (1986):
Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects.
Am. Rev. Respir. Dis.; 134: 986-989.

Hilman B.C., Bairnsfather L., Washburne W., Vekovius A.L. (1987):
Nebulized cromolyn sodium: safety, efficacy, and role in the management of childhood asthma.
Pediatr. Allergy Immunol.; 1: 43-52.

Hodsman A.B., Toogood J.H., Jennings B, Fraher L.J., Basrville J.C. (1991):
Differential effects of inhaled budesonide and oral prednisolone on serum osteocalcin.
J. Clin. Endocrinol. Metab.; 72: 530-540.

Holgate S.T., Beasley R., Twentyman O.P. (1987):
The pathogenesis and significance of bronchial hyperresponsiveness in airways disease.
Clin. Sci.; 73: 561-572.

Holtzman M.J., Fabbri L.M., O'Byrne P.M., Gold B.D., Aizawa H., Walters E.H., Alpert S.E., Nadel J.A. (1983):
Importance of airway inflammation for hyperresponsiveness induced by ozone.
Am. Rev. Respir. Dis.; 127: 686-690.

Honicky R.E., Osborne J.S. III, Apkom C.A. (1985):
Symptoms of respiratory illness in young children and the use of woodburning stoves for indoor heating.
Pediatrics; 75: 587-593.

Hopp R.J., Bewtra A.K., Nair N.M., Townley R.G. (1984):
Specificity and sensitivity of methacholine inhalation challenge in normal and asthmatic children.
J. Allergy Clin. Immunol.; 74: 154-158.

Horn B.R., Robin E.D., Theodore J. (1975):
Total eosinophil counts in the management of bronchial asthma.
N. Engl. J. Med.; 292: 1152-1155.

Ibrahim R.A., El Atrebi M. (1990):

Treatment of chronic maxillary sinusitis in relation to childhood asthma.
The New Egyptian Journal of Medicine; vol. 4 (2): 819-821.

Ilangovan P., Pedersen S., Godfrey S., Nikander K., Noviski N., Warner J.O. (1993):
Treatment of severe steroid dependent preschool asthma with nebulized budesonide suspension.
Arch. Dis. Child., 68: 356-359.

Inouye T., Tarlo S., Broder I., Covey I., Davies G., Leznoff A., Mintz S., Thomas P. (1985):
Severity of asthma in skin test-negative and skin test-positive patients.
J. Allergy Clin. Immunol.; 75: 313-319.

Irwin R.S., Curley F.J., French C.L. (1990):
Chronic cough the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy.
Am. Rev. Respir. Dis.; 141: 640-647.

Israel E, Fischer A.R., Rosenberg M.A., Lilly C.M., Callery J.C., Shapiro J., Cohn J., Rubin P., Drazen J.M. (1993):
The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin.
Am. Rev. Respir. Dis.; 148: 1447-1451.

Israel E., Cohn. J., Dube L., Drazen J.M. (1996):
Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma.
JAMA; 275: 931-936.

Jacobsen D.W. (1991):
Adverse reactions to food and food additives. In:
Metcalfe D.D., Sampson H.A., Simon R.A. (eds.): Food Allergy Adverse Reactions to Foods and Food Additives. Boston, Blackwell Scientific Publications, pp. 276-287.

Jeffrey P.K., Goodfrey R.W., Adelroth E., Nelson F., Rogers A., Johanson S.A. (1992):
Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma.
Am. Rev. Respir. Dis.; 145: 890-899.

Jennings B.H., Andersson K.E., Johansson S.A. (1991a):
The assessment of the systemic effects of inhaled glucocorticosteroids. The effects of inhaled budesonide vs. oral prednisolone on calcium metabolism.
Eur. J. Clin. Pharmacol.; 41: 11-16.

Jennings B.H., Andersson K.E., Johansson S.A. (1991b):
Assessment of systemic effects of inhaled glucocorticosteroids: comparison of the effects of inhaled budesonide and oral prednisolone on adrenal function and markers of bone turnover.
Eur. J. Clin. Pharmacol.; 40: 77-82.

Johnson D., Osborn L.M., (1991):
Cough variant asthma: A review of the clinical literature.
J. Asthma; 28: 85-90.

Johnston I.D.A., Bland J.M., Anderson H.R. (1987):
Ethnic variation in respiratory morbidity and lung function in childhood.
Thorax; 42: 542-548.

Josephs L.K., Gregg I., Holgate S.T. (1990):
Does non-specific bronchial hyperresponsiveness indicate the severity of asthma.
Eur.Respir. J.; 3: 220-227.

Josephs L.K., Gregg I., Mullee M.A., Holgate S.T. (1989):
Nonspecific bronchial reactivity and its relationship to the clinical expression of asthma: A longitudinal study.
Am. Rev. Respir. Dis.; 140: 350-357.

Juniper E.F., Frith P.A., Dunnett C., Cockroft D.W., Hargreave F.E. (1987):

Reproducibility and comparison of responses to inhaled histamine and methacholine.
Thorax; 33: 705-710.

Kaliner M.A. (1992):
Human nasal host defense and sinusitis.
J. Allergy Clin. Immunol.; 90 (3): 424-430.

Kaliner M., Lemanske R. (1992):
Rhinitis and asthma.
JAMA; 268: 2807-2829.

Kaliner M., Shelhamer J.H., Davis P.B., Smith L.J., Venter J.C. (1982):
Autonomic nervous system abnormalities and allergy.
Ann. Intern. Med.; 96: 349-357.

Kamada A.K., Szefler S.J. (1995):
Glucocorticoids and growth in asthmatic children.
Pediatr. Allergy Immunol.; 6: 145-154.

Kamada A.K., Szefler S.J., Martin R.J., Boushey H.A., Chinchilli V.M., Drazen J.M., Fish J.E., Israel E., Lazarus S.C., Lemanske R.F. and the Asthma Clinical Research Network (1996):
Issues in the use of inhaled glucocorticoids.
Am. J. Respir. Crit. Care Med.; 153: 1739-1748.

Kaplan E.S., Hoyt N.J. (1982):
Nosocomial sinusitis.
JAMA; 247: 839.

Karma P., Pukander J., Penttila M., Ylikoski J., Savolainen S., Olen L., Melen I., Loth S. (1991):
The comparative efficacy and safety of clarithromycin and amoxycillin in the treatment of outpatients with acute maxillary sinusitis.
J. Antimicrob. Chemotherapy; 27 (Suppl. A): 83-90.

Kasper W.J., Howe P.M. (1990):

Fatal varicella after a single course of corticosteroids.
Pediatr. Infect. Dis. J.; 9: 729-732.

Katzenstein A.A., Sale S.R., Greenberger P.A. (1983):
Allergic Aspergillus sinusitis:
A newly recognized form of sinusitis.
J. Allergy Clin. Immunol.; 72 (1): 89-93.

Kavanagh K.T., Hughes W.T., Parham D.M., chanin L.R. (1991):
Fungal sinusitis in immunocompromised children with neoplasms.
Ann. Otol. Rhinol. Laryngol.; 100: 331-336.

Kay A.B. (1991):
Asthma and inflammation.
J. Allergy Clin. Immunol.; 87: 893-910.

Kelly W.J.W., Hudson I., Phelan P.D., Pain M.C., Olinsky A. (1987):
Childhood asthma in adult life: A further study at 28 years of age.
BMJ; 294: 1059-1062.

Kelly W.J.W., Hudson I., Phelan P.D., Pain M.C., Olinsky A. (1990):
Atopy in subjects with asthma followed to the age of 28 years.
J. Allergy Clin. Immunol.; 85: 548-557.

Kelly W.J.W., Hudson I., Raven J., Pain M.C., Olinsky A. (1988):
Childhood asthma and adult lung function.
Am. Rev. Respir. Dis.; 138: 26-30.

Kemp J.P., Dockhorn R.J., Busse W.W., Bleecker E.R., Van As A (1994):
Prolonged effect of inhaled salmeterol against exercise-induced bronchospasm.
Am. J. Respir. Crit. Care Med.; 150:1612-1615.

Kennedy D.W. (1990):
Surgical update.

Otolaryngol. Head Neck Surg.; 103 (5): 884-886.

Kerrebijn K.F.(1990):
Use of topical corticosteroids in the treatment of childhood asthma.
Am. Rev. Respir. Dis.; 141: 577-581.

Kerrebijn K.F., van Essen-Zandvliet E.E., Neijens H.J. (1987):
Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma.
J. Allergy Clin. Immunol.; 79(4): 653-659.

Kerstjens H.A., Brand P.L., Hughes M.D., Robinson N.J., Postma D.S., Sluiter H.J., Bleecker E.R., Dekhuijzen P.N., de Jomg P.M., Mengelers H.J. et al.(1992):
A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease.
N. Engl. J. Med.; 327: 1413-1419.

Khot A., Burn R., Evans N., Lenney W., Storr J. (1988):
Biometeorologic triggers in childhood asthma.
Clin. Allergy; 18: 351-358.

Kidney J., Dominguez M., Taylor P.M., Rose M., Chung K.F., Barnes P.J. (1995):
Immunomodulation by theophylline in asthma.
Am. J. Respir. Crit. Care Med.; 151: 1907-1914.

Kingston H.G., Hirshman C.A. (1984):
Perioperative management of the patient with asthma.
Anesth. Analg.; 63: 844-855.

Kinsman R.A., Dahlem N.W., Spector S.L., Standenmoyer H. (1977):
Observations on subjective symptomatology, coping behavior and medical decisions in asthma.
Psychosom. Med.; 39:102-119.

Kjellman N.M., Johanson S.G., Roth A. (1976):

Serum IgE levels in healthy children quantified by a sandwich technique.
Clin. Allergy; 6 (1): 51-59.

Kleijnen J., Riet G., Knpschild P. (1991):
Acupuncture and asthma: a review of controlled trials.
Thorax; 46: 799-802.

Kovatch A.L., Wald E.R., Ledesma-Medina J., Chiponis D.M., Bedingfield B. (1984):
Maxillary sinus radiographs in children with nonrespiratory complaints.
Pediatrics; 73: 306-308.

Kuhn J.P. (1986):
Imaging of the paranasal sinuses: current status.
J. Allergy Clin. Immunol.; 77 (1): 6-8.

Kupferberg S.B., Bent J.P. 3rd., Kuhn F.A. (1997):
Prognosis for allergic fungal sinusitis.
Otolaryngol. Head Neck Surg.; 117 (1): 35-41.

Laberge S., Ernest P., Ghaffar O., Cruikshank W.W., Kornfeld H., Center D.M., Hamid Q. (1997):
Increased expression of interleukin-16 in bronchial mucosa of subjects with atopic asthma.
Am. J. Respir. Cell Mol. Biol.; 17 (2): 193-202.

Laitinen L.A., Heino M., Laitinen A., Kava T., Haahtela T. (1989):
Damage of the airway epithelium and bronchial reactivity in patients with asthma.
Am. Rev. Respir. Dis.; 131: 599-606.

Lal S., Dorow P.D., Venho K.K., Chatterjee S.S. (1993):
Nedocromil sodium is more effective than cromolyn sodium for the treatment of chronic
reversible obstructive airway disease.
Chest; 104: 438-447.

Lam S., Wong R., Yeung M. (1979):
Nonspecific bronchial reactivity in occupational asthma.
J. Allergy Clin. Immunol.; 63: 28-34.

Landman M.D. (1986):
Ultrasound screening for sinus disease.
Otolaryngol. Head Neck Surg.; 94 (2): 157-164.

Lanza D.C., Kennedy D.W. (1992):
Current concepts in the surgical management of chronic and recurrent acute sinusitis.
J. Allergy Clin. Immunol.; 90 (3): 505-510.

Lawlor G.J.Jr., Tashkin D.P. (1995):
Asthma. In:
Lawlor G.J.Jr., Fischer T.J., Adelman D.C. (eds.). Manual of Allergy and Immunology. Third edition. Little, Brown and Company, pp.: 121-180.

Lee D.A., Winslow N.R., Speight A.N.P., Hey E.N. (1983):
Prevalence and spectrum of asthma in childhood.
BMJ; 286: 1256-1258.

Lemanske R.F. (1992):
Mechanisms of airway inflammation.
Chest; 101: 372S-377S.

Lichtenstein D., Biderman P., Merziere G., Gepner A. (1998):
The "sinusogram", a real-time ultrasound sign of maxillary sinusitis.
Intensive Care Med.; 24(10): 1057-1061.

Litchfield T.M., Lee T.H. (1992):
Asthma: Cells and cytokines.
J. Asthma; 29: 181-191

Lockey R.F., Benedict L.M., Turkeltaub P.C., Bukantz S.C. (1987):
Fatalities from immunotherapy (IT) and skin testing (ST).
J. Allergy Clin. Immunol.; 79: 660-677.

Lusk R.P. (1992):
Surgical modalities other than ethmoidectomy.
J. Allergy Clin. Immunol.; 90 (3): 538-542.

Lusk R.P., Lazar R.H., Muntz H.R. (1989):
The diagnosis and treatment of recurrent and chronic sinusitis in children.
Pediatr. Clin. North Am.; 36 (6): 1411-1421.

Mabry L. (1990):
Pharmacotherapy with immunotherapy for the treatment of otolaryngologic allergy.
Ear Nose Throat J.; 69: 63-71.

Mabry R.L. (1991):
Use and misuse of cromolyn and corticosteroids.
Am. J. Rhinol.; 5: 121-124.

Mabry R.L., Marple B.F., Folker R.J., Mabry C.S. (1998):
Immunotherapy for allergic fungal sinusitis: three years' experience.
Otolaryngol. Head Neck Surg.; 119(6): 648-651.

Magnan A., van Pee D., Bongrand P., Vervloet D. (1998):
Alveolar macrophage interleukin (IL)-10 and IL-12 production in atopic asthma.
Allergy; 53 (11): 1092-1095.

Mak H., Johnston P., Abbey H., Talamo R.C. (1982):
Prevalence of asthma and health service utilization of asthmatic children in an inner city.
J. Allergy Clin. Immunol.; 70: 367-372.

Malow J.B., Creticos C.M. (1989):
Nonsurgical treatment of sinusitis.
Otol. Clin. North. Am.; 22 (4): 809-818.

Manning S.C. (1992):
Surgical management of sinus disease in children.

Ann. Otol. Rhinol. Laryngol.; 101: 42-45.

Manning S.C., Wasserman R.L., Silver R., Philips D.L. (1994):
Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma.
Arch Otolaryngol. Head Neck Surg.; vol 120: 1142-1145.

Maresh M.M., Washburn A.H. (1940):
Paranasal sinuses from birth to late adolescence: clinical and roentgenographic evidence of infection.
Am. J. Dis. Child.; 60:841.

Martin A.J., Landau L.I., Phelan P.D. (1981):
Natural history of allergy in asthmatic children followed to adult life.
Med. J. Aust.; 2: 470-474.

Martin A.J., Landau L.I., Phelan P.D. (1982):
Predicting the course of asthma in children.
Aust. Paediatri.; 18: 84-87.

Martin A.J., Landau L.I., Phelan P.D. (1982):
Asthma from childhood at age 21: The patient and his disease.
BMJ; 284: 380-382.

Martinez F.D. (1995):
Viral infections and the development of asthma.
Am. J. Respir. Crit. Care Med.; 151: 1644-1647.

Martinez F.D., Antognoni G., Macri F., Bonci E., Midulla F., De Castro G., Ronchetti R. (1988):
Parental smoking enhances bronchial responsiveness in nine-year old children.
Am. Rev. Respir. Dis.; 138: 518-523.

Martinez F.D., Morgan W.J., Wright A.L., Holberg C.J., Taussig L.M. (1988):
Diminished lung function as a predisposing factor for wheezing respiratory illnesses in infants.
N. Engl. J. Med.; 319: 1112-1117.

McConnochie K.M., Roghman K.J. (1984):
Bronchiolitis as a possible cause of wheezing in childhood: New evidence.
Pediatrics; 74: 1-10.

McFadden E.R. Jr. (1986):
Nasal sinus-pulmonary reflexes and bronchial asthma.
J. Allergy Clin. Immunol.; 78: 1-3.

McFadden E.R. Jr., Gilbert I.A. (1992):
Asthma.
N. Engl. J. Med.; 327: 1928-1937.

McFadden E.R. Jr., Gilbert I.A. (1994):
Exercise-induced asthma.
N. Engl. J. Med.; 330: 1362-1367.

McFadden E.R., Kiser R., DeGroot W.J. (1973):
Acute bronchial asthma: Relationships between clinical and physiological manifestations.
N. Engl. J. Med.; 288: 221-225.

McFadden E.R., Lyons H.A. (1968):
Arterial blood gas tension in asthma.
N. Engl. J. Med.; 278: 1027-1032.

Melia R.J., Florey C.D., Altman D.G., Swan A.V. (1977):
Association between gas cooking and respiratory disease in children.
BMJ; 2: 149-152.

Meltzer S.S., Hasday J.D., Cohn J., Bleecker E.R. (1996):
Inhibition of exercise-induced bronchospasm by zileuton: a 5-lipoxygenase inhibitor.
Am. J. Respir. Crit. Care Med.; 153: 931-935.

Mendoza G.R. (1991):
Peak flow monitoring.
J. Asthma; 28: 161-177.

Mings R., Friedman W.H., Linford P.A., Slavin R.G. (1988):
Five-year follow-up of the effects of bilateral intranasal sphenoethmoidectomy in patients with sinusitis and asthma.
Am. J. Rhinol.; 2: 13-16.

Montefort S., Herbert C.A., Robinson C., Holgate S.T. (1992):
The bronchial epithelium as a target for inflammatory attack in asthma.
Clin. Exp. Allergy; 22: 511-520.

Montgomery G.L., Tepper R.S. (1990):
Changes in airway reactivity with age in normal infants and young children.
Am. Rev. Respir. Dis.; 142: 1372-1376.

Moq J.Y.Q., Simpson H. (1982):
Outcome of acute lower respiratory tract infections in infants: Preliminary report of seven-year follow-up.
B.M.J.; 285: 333-337.

Morice A. (1986):
Adulterated "homeopathic" care for asthma.
Lancet; 1: 862-863.

Mrazek D.A. (1988):
Asthma: Psychiatric considerations, evaluation and management. In:
Middleton E., Reed C.E., Ellis E.F. et al. (eds.): Allergy Principles and Practice. St. Louis, Mosby, pp. 1176-1196.

Mrazek D.A.(1992):
Psychiatric complications of pediatric asthma.
Ann. Allergy; 69: 285-290.

Mrazek D.A., Klinnert M.D., Mrazek P., Marcey T. (1991):
Early asthma onset: Consideration of parenting issues.
J. Am. Acad. Child Adolescent Psych.; 30: 277-282.

Mueller G.A., Eigen H. (1992):

Pediatric pulmonary function testing in asthma.
Pediatr. Clin. North Am., 39 (6): 1243-1258.

Muntz H.R., Lusk R.P. (1991):
Bacteriology of the ethmoid bulla in children with chronic sinusitis.
Arch. Otolaryngol. Head Neck Surg.; 117: 179-181.

Murray A.B., Ferguson A.C. (1983):
Dust-free bedrooms in the treatment of asthmatic children with house dust or house-dust mite allergy: A controlled trial.
Pediatrics; 71: 418-422.

Murray A.B., Morrison B.J. (1986):
The effect of cigarette smoke from the mother on bronchial hyperresponsiveness and severity of symptoms in children with asthma.
J. Allergy Clin. Immunol.; 77: 575-581.

Murray A.B., Morrison B.J. (1988):
Passive smoking and the seasonal difference of severity of asthma in children.
Chest; 94: 701-708.

Murray M., Webb M.S.C., O'Callaghan C., Swarbrick A.S., Milner A.D. (1992):
Respiratory status and allergy after bronchiolitis.
Arch. Dis. Child.: 67: 482-487.

Naclerio R.M. (1991):
Allergic rhinitis.
New Engl. J. Med.; 325: 860-869.

Nassif E.G., Weinberger M., Thompson R, Huntley W. (1981):
The value of maintenance theophylline in steroid-dependent asthma.
N. Engl. J. Med.; 304: 71-75.

Nastasi K.J., Heinly T.L., Blaiss M.S. (1995):
Exercise-induced asthma and the athlete.

J. Asthma; 32:249-257.

Neddenriep D., Martinez F. and Morgan (1990):
Increased specific lung compliance in newborns whose mothers smoked during pregnancy.
Am. Rev. Respir. Dis.; 141: A282.

Neddenriep D., Schmacher M.J., Lemen R.J. (1989):
Asthma in childhood.
Curr. Probl. Pediatr.; 19: 325-388.

Nelson H.S. (1985):
The atopic diseases.
Ann. Allergy; 55: 441-447.

Nelson H.S., Hirsch R.S., Ohman J.L. Jr., Platts-Mills T.A., Reed C.E., Solomon W.R. (1988):
Recommendations for the use of residential air-cleaning devices in the treatment of allergic respiratory diseases.
J. Allergy Clin. Immunol.; 82: 661-669.

Nelson H.S., Weber R.W. (1988):
Endocrine aspects of allergic diseases. In:
Bierman C.W., Pealman D.S. (eds.). Allergic Disease From Infancy to Adulthood. Philadelphia: W.B. Saunders, ch. 15.

Newman K.B., Mason U.G., Buchmeler A., Schmaling K.B., Corsello P., Nelson H.S. (1997):
Failure of colchicine to reduce inhaled triamcinolone in patients with asthma.
J. Allergy Clin. Immunol.; 99: 176-178.

Nielsen-Kudsk J.E., Mellemkjaer S., Siggaard C, Nielsen C.B. (1988):
Effects of pinacidil on guinea-pig airway smooth muscle contracted by asthma mediators.
Eur. J. Pharmacol.; 157:221-226.

Ninan T.K., Russell G. (1992):
Asthma, inhaled corticosteroid treatment and growth.

Arch Dis. Child.; 67(6): 703-705.

N.H.L.B.I.: National Heart, Lung and Blood Institute (1996):
Working Group Report: Considerations for Diagnosing and Managing Asthma in the Elderly.
National Institutes of Health publications; 96-3662.

Norman P.S., VanMetre T.E. (1990):
The safety of allergenic immunotherapy.
J. Allergy Clin. Immunol.; 85: 522-525.

November E., De Martino M., Vierucci A (1988):
Foods and respiratory allergy.
J. Allergy Clin. Immunol.; 81: 1059.

November G., Frongia G.F., Veneruso G., Vierucci A. (1994):
Inhibition of exercise-induced asthma (EIA) by nedocromil sodium and sodium cromoglycate in children.
Pediatr. Allergy Immunol.; 5: 107-110.

Nguyen K.L., Corbett M.L., Garcia D.P., Eberly S.M., Massey E.N., Le H. T., Shearer L.T., Karibo J.M., Pence H.L. (1993):
Chronic sinusitis among pediatric patients with chronic respiratory complaints.
J. Allergy Clin. Immunol.; 92: 824-830.

O'Byrne P.M., Dolovich J., Hargreave F.E. (1987):
Late asthmatic responses.
Am. Rev. Respir. Dis.; 186: 740-751.

O'Byrne P.M., Hargreave F.E., Kirby J.G. (1987):
Airway inflammation and hyperresponsiveness.
Am. Rev. Respir. Dis.; 136: 535-537.

O'Byrne P.M., Ryan G., Morris M., McCormack D., Jones N.L., Morse J.L., Hargreave F.E. (1982):
Asthma induced by cold air and its relation to nonspecific bronchial responsiveness to methacholine.
Am. Rev. Respir. Dis.; 125: 281-285.

O'Conner G.T., Sparrow D., Segal M.R., Weiss S.T. (1989):
Smoking, atopy and methacholine airway responsiveness among middle aged and elderly men.
Am. Rev. Respir. Dis.; 140: 1520-1526.

O'Hickey S.P., Rees P.J. (1994):
High-dose nedocromil sodium as an addition to inhaled corticosteroids in the treatment of asthma.
Respir. Med.; 88: 499-502.

Ohman J.L. Jr. (1989):
Allergen immunotherapy in asthma: Evidence for efficacy.
J. Allergy Clin. Immunol.; 84: 133-140.

Orehek J., Massari J.P., Gayrard P., Grimaud C., Charpin J. (1976):
Effect of short-term, low level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients.
J. Clin. Invest.; 57: 301-307.

Orenstein S.R., Orenstein D.M. (1988):
Gastroesophageal reflux and respiratory disease in children.
J. Pediatr.; 112:847-858.

Packe G.E., Archer P. StJ., Ayres J.G. (1983):
Asthma and the weather.
Lancet; 2: 281.

Packe G.E., Douglas J.G., McDonald A.F., Robins S.P., Reid D.M. (1992):
Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate
and intermittent systemic corticosteroids.
Thorax; 47(6): 414-417.

Park E.S., Golding J., Carswell F., Stewart-Brown S. (1986):
Preschool wheezing and prognosis at 10.
Arch. Dis. Child.; 61: 642-646.

Parnes L.S., Brown D.H., Garcia B. (1989):

Mycotic sinusitis: a management protocol.
J. Otolaryngol.; 18 (4): 176-180.

Parsons D.S., Phillips S.E. (1993):
Functional endoscopic surgery in children: a retrospective analysis of results.
Laryngoscope; 103: 899-903.

Pattemore P.K., Asher M.I., Harrison A.C., Mitchell E.A., Rea H.H., Stewart A.W. (1990):
The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma and asthma symptoms.
Am. Rev. Respir. Dis.; 142: 549-554.

Pattemore P.K., Johnston S.L., Bardin P.G. (1992):
Viruses as precipitants of asthma symptoms. I. Epidemiology.
Clin. Exp. Allergy; 22: 325-336.

Peat J.K., Britton W.J., Salome C.M., Woolcock A.J. (1987):
Bronchial hyperresponsiveness in two populations of Australian schoolchildren. II. Relative importance of associated factors.
Clin. Allergy;17: 283-290.

Peat J.K., Britton W.J., Salome C.M., Woolcock A.J. (1987):
Bronchial hyperresponsiveness in two populations of Australian schoolchildren. III. Effect of exposure to environmental allergens.
Clin. Allergy; 17: 291-300.

Peat J.K., Salome C.M., Toelle B.G., Bauman A., Woolcock A.J. (1992):
Reliability of a respiratory history questionnaire and effect of mode of administration on classification of asthma in children.
Chest; 102: 153-157.

Peat J.K., Woolcock A.J. (1991):
Sensitivity to common allergens: Relation to respiratory symptoms and bronchial hyperresponsiveness in children from three different climatic areas of Australia.
Clin. Exp. Allergy; 21: 573-581.

Pedersen S., Hansen O.R. (1995):
Budesonide treatment of moderate and severe asthma in children: a dose-response study.
J. Allergy Clin. Immunol.; 95: 29-33.

Pharmacology on line (1999):
Zileuton.
http://www.cponline.com.

Phipatanakul C.S., Slavin R.G. (1974):
Bronchial asthma produced by paranasal sinusitis.
Arch. Otolaryngol. Head Neck Surg.; 100: 109-112.

Pierson W.E. (1991):
Treatment of the asthmatic athlete.
Immunol. Allergy Clin. North. Am., 11: 143-151.

Pierson W.E., Koenig J.Q. (1992):
Respiratory effects of air pollution on allergic disease.
J. Allergy Clin. Immunol.; 90: 557-566.

Platts-Mills T.A.E. (1992):
Controlling indoor allergens in patients with asthma.
J. Respir. Dis.; 13: S20-S27.

Platts-Mills T.A.E., Tovey E.R., Mitchell E.B., Moszoro H., Nock P., Wilkins S.R. (1982):
Reduction of bronchial hyperreactivity during prolonged allergen avoidance.
Lancet; 2: 675-678.

Pullan C.R., Hey E.N. (1982):
Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy.
BMJ; 284: 1665-1669.

Polmar S.H. (1992):
The role of the immunologist in sinus disease.
J. Allergy Clin. Immunol.; 90 (3): 511-514.

Quackenboss J.J., Lebowitz M.K. (1991):
The normal range of diurnal changes in peak expiratory flow rates: Relationship to symptoms and respiratory disease.
Am. Rev. Respir. Dis.; 143: 323-330.

Rachelefsky G.S., Katz R.M., Siegel S.C. (1984):
Chronic sinus disease with associated reactive airway disease in children.
Pediatrics; 73: 526-529.

Rachelefsky G.S., Goldberg M., Katz R.M., Boris G., Gyepes M.T., Shapiro M.J., Mickey M.R., Finegold S.M., Siegel S.C. (1978):
Sinus disease in children with respiratory allergy.
J. Allergy Clin. Immunol.; 61: 310.

Ramesh S., Brodsky L., Afshani E., Pizzuto M., Ishman M., Helm J., Ballow M. (1997):
Open trial of intravenous immune serum globulin for chronic sinusitis in children.
Ann. Allergy Asthma Immunol.; 79(2): 119-124.

Ramsey B., Richardson M.A. (1992):
Impact of sinusitis in cystic fibrosis.
J. Allergy Clin. Immunol.; 90 (3): 547-551.

Rebuck A.S., Read J. (1971):
Assessment and management of severe asthma.
Am. J. Med.; 51: 788-790.

Reid M.J. (1992):
Complicating features of asthma.
Pediatric Clinics of North America; vol. 39 (6): 1327-1341.

Reilly D.T., McSharry C., Taylor M.A., Aitchison T. (1986):
Is homeopathy a placebo response? Controlled trial of homeopathic potency, with pollen in hayfever as model.
Lancet; 2: 881-886.

Reilly J.S. (1990):
The sinusitis cycle.
Otolaryngol. Head Neck Surg.; 103(5): 856-862.

Reisman R.E., Mauriello P.M., Davis G.B. (1990):
A double-blind study of the effectiveness of a high-efficiency particulate air (HEPA) filter in the treatment of patients with perennial allergic rhinitis and asthma.
J. Allergy Clin. Immunol.; 85: 1050-1057.

Reynolds R.C., Catlin R.I., Cluff L.E. (1964):
Bacteriology and antibiotic treatment of acute maxillary sinusitis.
Bull. Johns Hopkins Hosp.; 114: 269.

Richards W., Roth R., Church J. (1991):
Underdiagnosis and undertreatment of chronic sinusitis in children.
Clinical Pediatrics; vol. 30 (2): 88-92.

Richtsmeier W.J. (1992):
Medical and surgical management of sinusitis in adults.
Ann. Otol. Rhinol. Laryngol.; 101: 46-50.

Rinehart J.J., Sagone A.L., Balcerzak S.P., Ackerman G.A., LaBuglio A.F. (1975):
Effects of corticosteroid therapy on human monocyte fuction.
N. Engl. J. Med.: 292: 236-241.

Robinson D.S., Hamid Q., Ying S., Tsicopoulos A., Barkans J., Bentley A.M., Corrigan C., Durham S.R., Kay A.B. (1992):
Predominant TH2-like bronchoalveolar T-Lymphocyte population in atopic asthma.
N. Engl. J. Med.; 326: 298-304.

Rochester C.L., Rankin J.A. (1991):
Is asthma T-cell mediated?
Am. Rev. Respir. Dis.; 144: 1005-1007.

Rohr A.S, Spector S.L., Siegel S.C., Katz R.M., Rachelefsky G.S. (1986):

Correlation between A-mode ultrasound and radiography in the diagnosis of maxillary sinusitis.
J. Allergy Clin. Immunol.; 78 (1): 58-61.

Romagnani S. (1994):
Regulation of the development of type 2 T-helper cells in allergy.
Current opinion in Immunology; 6: 838-846.

Rubinfeld A.R., Pain M.C.F. (1977):
How mild is mild asthma?
Thorax ; 32: 177-181.

Ryan G., Latimer K.M., Dolovich J., Hargreave F.E. (1982):
Bronchial responsiveness to histamine: Relationship to diurnal variation of peak flow rates, improvement after bronchodilator and airway calibre.
Thorax ; 37: 423-429.

Samet J.M., Marbury M.C., Spengler J.D. (1987):
Respiratory effects of indoor air pollution.
J. Allergy Clin. Immunol.; 79: 685-700.

Schatz M., Zeiger R.S., Harden K.M., Hoffman C.P., Forsythe A.B., Chilingar L.M., Porreco R.P., Benenson A.S., Sperling W.L., Saunders B.S. et al. (1988):
The safety of inhaled beta-2 agonist bronchodilators during pregnancy.
J. Allergy Clin. Immunol.; 82: 686-695.

Schober G., Kniest F.M., Kort H.S., De Saint Georges Gridelet D.M., Van Bronswick J.E. (1992):
Comparative efficacy of house dust mite extermination products.
Clin. Exp. Allergy; 22: 618-626.

Schumacher M.J., Cota K.A., Taussig L.M. (1986):
Pulmonary response to nasal-challenge testing of atopic subjects with stable asthma.
J. Allergy Clin. Immunol.; 78: 30-35.

Schwartz H.J., Thompson J.S., Sher T.H., Ross R.J. (1987):

Occult sinus abnormalities in the asthmatic patient.
Arch Intern. Med.; 147: 2194-2196.

Schwartz H.J., Blumenthal M., Brady R., Braun S., Lockey R., Myers D., Mansfiald L., Mullarkey M., Owens G., Ratner P., Repsher L., van As A. (1996):
A comparative study of the clinical efficacy of nedocromil sodium and placebo.
Chest; 109: 945-952.

Schwartz J., Gold D., Dockery D.W. (1990):
Predictors of asthma and persistent wheeze in a national sample of children in the United States.
Am. Rev. Respir. Dis.; 142: 555-562.

Schwartz J.D., Katz S.A., Fegley R.W., Tockman M.S. (1988):
Analysis of spirometric data from a national sample of health: 6-24 year olds (NHANES II).
Am. Rev. Respir. Dis.; 138: 1405-1414.

Schwartz L.B. (1994):
Mast cells: Function and contents.
Current opinion in Immunology; 6: 91-91.

Sears M.R. (1991):
Epidemiological trends in bronchial asthma. In:
Kaliner M.A., Barnes P.J., Persson CGA (eds.): Asthma: Its Pathology and Treatment.
New York, Marcel Dekker, Inc., pp. 1-49.

Sears M.R., Burrows B., Flannery E.M., Herbison G.P., Hewitt C.J., Holdaway M.D. (1991):
Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children.
N. Engl. J. Med.; 325: 1067-1071.

Sears M.R., Herbison G.P., Holdaway M.D., Hewitt C.J., Flannery E.M., Silva P.A. (1989):
The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma.

Clin. Exp. Allergy; 19: 419-424.

Sears M.R., Jones D.T., Holdaway M.D., Hewitt C.J., Flannery E.M., Herbison G.P., Silva P.A. (1986):
Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children.
Thorax; 41: 283-289.

Sears M.R., Taylor D.R., Print C.G., Lake D.G., Li Q.Q., Flannery E.M., Yates D.M., Lucas M.K., Herbison G.P. (1990):
Regular inhaled beta 2-agonist treatment in bronchial asthma.
Lancet; 336: 1391-1396.

Seltroos O, Halme M. (1991):
Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler.
Thorax; 46: 891-894.

Settipane G.A., Chafee F.H. (1977):
Nasal polyps in asthma and rhinitis: a review of 6037 patients.
J. Allergy Clin. Immunol.; 59: 17-21.

Settipane G.A., Schoenfeld E., Hamolsky M.W. (1972):
Asthma and hyperthyroidism.
J. Allergy; 49: 348-355.

Shamssain M.H., Shamsian N. (1999):
Prevalence and severity of asthma, rhinitis and atopic eczema: the north east study.
Arch. Dis. Child.; 81: 313-317.

Shannon M., Lovejoy F.H. (1990):
The influence of age vs. peak serum concentration on life-threatening events after chronic theophylline intoxication.
Arch. Intern. Med.; 150: 2045-2048.

Shatz M., Harden K.M., Forsythe A., Chilingar L., Hoffman C., Sperling W., Zeiger R.S. (1988):

The course of asthma during pregnancy, postpartum and with successive pregnancies: A prospective analysis.
J. Allergy Clin. Immunol.; 81: 509-517.

Shaw N.J., Edmunds A.T. (1986):
Inhaled beclomethasone and oral candidiasis.
Arch. Dis. Child.; 61: 788-790.

Shelhamer J.H., Metcalfe D.D., Smith L.J., Kaliner M. (1980):
Abnormal beta-adrenergic responsiveness in allergic subjects: analysis of isoproterenol-induced cardiovascular and plasma cyclic adenosine monophosphate responses.
J. Allergy Clin. Immunol.; 66: 52-60.

Sibbald B., Horn M.E.C., Gregg I. (1980):
A family study of the genetic basis of asthma and wheezy bronchitis.
Arch. Dis. Child.; 54: 354-357.

Siegel S.C., Rachelefsky G.S. (1985):
Asthma in infants and children. Part 1.
J. Allergy Clin. Immunol.; 76: 1-15.

Simons F.E., Persaud M.P., Gillespie C.A., Cheang M, Shuckett E.P. (1993):
Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids.
Lancet; 342: 776-778.

Simon R.A. (1984):
Adverse reactions to drug additives.
J. Allergy Clin. Immunol.; 74: 623-630.

Slavin R.G. (1982):
Relationship of nasal disease and sinusitis to bronchial asthma.
Ann. Allergy; 49: 76.

Slavin R.G. (1988):
Sinusitis in adults.
J. Allergy Clin. Immunol.; 81: 1028.

Slavin R.G. (1991):
Sinusitis- present state of the art.
Allergy Proc.; 12: 163-165.

Slavin R.G. (1991):
Recalcitrant asthma: Could sinusitis be the culprit?
J. Respir. Dis.; 12: 182-194.

Slavin R.G. (1992):
Asthma and sinusitis.
J. Allergy Clin. Immunol.; 90 : 534-537.

Slavin R.G., Linford P.A., Friedman W.H. (1983):
Sphenoethmoidectomy in the treatment of nasal polyps, sinusitis and bronchial asthma.
J. Allergy Clin. Immunol.; 71: 156-162.

Slavin R.G., Ziliox A.P., Samuels L.D. (1988):
Is there such an entity as allergic sinusitis?
J. Allergy Clin. Immunol.; 81: 224.

Sluder G. (1919):
Asthma as a nasal reflex.
JAMA; 73: 589.

Sly R.M. (1996):
Allergic disorders. In:
Behrman R.E., Kliegman R.M., Arvin M. (eds.): Nelson Textbook of Pediatrics. 15th edition. Philadelphia: W.B. Saunders, ch. 11, pp. 570-610.

Smith J.M. (1989):
Epidemiology and natural history of asthma, allergic rhinitis and atopic dermatitis (eczema). In:
Middleton E., Ellis E., Reed C.E. (eds.): Allergy Principles and Practice. 3rd. ed. St. Louis, Mosby, pp. 891-929.

Smith L. (1993):
Childhood asthma: diagnosis and treatment.

Curr. Probl. Pediatrics; 23: 271-305.

Spector S.L., Wagaard C.H., Farr R.S. (1979):
Aspirin and concomitant idiosyncracies in adult asthmatic patients.
J. Allergy Clin. Immunol.; 64: 500-506.

Speight A.N.P., Lee D.A. and Hey E.N. (1983):
Underdiagnosis and undertreatment of asthma in childhood.
BMJ; 286: 1253-1256.

Spiropoulos K., Stevens J., Eigen H, Spiropoulos A. (1986):
Specificity and sensitivity of methacholine challenge test in children with normal and hyperreactive airways.
Acta Paediatr. Scand.; 75: 737-743.

Spitzer W.O., Suissa S., Emst P., Horwitz R.I., Habbick B., Cockcroft D., Boivin J.E., McNutt M., Buist A.S., Rebuck A.S. (1992):
The use of beta-agonist and the risk of death and near death from asthma.
N. Engl. J. Med.; 326: 501-506.

Sporik R., Holgate S.T., Cogswell J.J. (1991):
Natural history of asthma in childhood: A birth cohort study.
Arch. Dis. Child.; 66: 1050-1053.

Sporik R., Holgate S.T., Platts-Mills T.A.E. (1990):
Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood.
N. Engl. J. Med.; 323: 502-507.

Stafford C.T. (1990):
The clinician's view of sinusitis.
Otolaryngol. Head Neck Surg.; 103 (5): 870-875.

Stammberger H. (1985):
Endoscopic surgery for mycotic and chronic recuring sinusitis.
Ann. Otol. Rhinol. Laryngol. Suppl.; 119:1-11.

Stevenson D.D., Simon R.A., Lumry W.R., Mathison D.A. (1986):
Adverse reactions to tartrazine.
J. Allergy Clin. Immunol.; 78: 182-198.

Storms W.W. (1991):
Clinical experiences with triamcinolone in rhinitis.
J. Respir. Dis. Suppl.; 12: S34-S39.

Strunk R.C. (1993):
Death due to asthma.
Am. Rev. Respir. Dis.; 148: 550-552.

Strunk R.C., Mrazek D.A., Wolfson-Fuhrman G.S., LaBrecque J.F. (1985):
Physiological and psychological characteristics associated with deaths due to asthma in childhood: A case- controlled study.
JAMA; 254:1193-1198.

Su W., Liu C., Hung S.Y., Tsai W.F. (1983):
Bacteriological study in chronic maxillary sinusitis.
Laryngoscope; 93: 931.

Suissa S, Ernest P., Boivin J.P., Horwitz R.I., Habbick B., Cockroft D., Blais L., McNutt M., Buist A.S., Spitzer W.O. (1994):
A cohort analysis of excess mortality in asthma and the use of inhaled beta$_2$-agonist.
Am. J. Respir. Crit. Care Med.; 149: 604-610.

Sultan M., Gaafar M., Abdel Satar B. and Mohy El Din Z. (1992):
Common allergens in asthmatic children in Sharkia Governorate.
The New Egyptian Journal of Medicine; vol. 7 (6): 1175-1179.

Supramaniam G., Warner J.O. (1986):
Artificial food additive intolerance in patients with angioedema and urticaria.
Lancet; 1: 907-909.

Sussman G.L., Beezhold D.H. (1995):
Allergy to latex rubber.
Ann. Intern. Med.; 122: 43-46.

Szefler S.J. (1991):
Glucocorticoid therapy for asthma: Clinical pharmacology.
J. Allergy Clin. Immunol.; 88: 147-165.

Szentivanyi A (1968):
The beta-adrenergic theory of the atopic abnormality in bronchial asthma.
J. Allergy Clin. Immunol.; 42: 203-220.

Tabachnik E., Zasik Z. (1991):
Diurnal cortisol secretion during therapy with inhaled beclomethasone dipropionate in children with asthma.
J. Pediatr.; 118: 294-297.

Tattersfield A.E., Higgins B.G. (1988):
Bronchial reactivity in the community.
Eur. Respir. J.; 1: 476-491.

Taussig L.M., Smith S.M., Blumenfeld R. (1981):
Chronic bronchitis in childhood: What is it?
Pediatrics; 67: 1-5.

Taylor S.L., Bush R.K., Selner J.C., Nordlee J.A., Wiener M.B., Holden K., Koepke J.W., Busse W.W. (1988):
Sensitivity to sulfited foods among sulfite-sensitive subjects with asthma.
J. Allergy Clin. Immunol.; 81: 1159-1167.

Tepper R.S. (1987):
Airway reactivity in infants: A positive response to methacholine and metaproterenol.
J. Appl. Physiol.; 62: 1155-1159.

Tepper R.S., Morgan W.J., Cota K., Wright A., Taussig L.M. (1986):

Physiological growth and development of the lung during the first year of life.
Am. Rev. Respir. Dis.; 134: 513-519.

The International Study of Asthma and Allergies in Childhood (ISAAC). Multi-centre study (1998):
Worldwide variations in the prevalence of asthma symptoms.
Eur. Respir. J.; 12 (2): 315-335.

Tinkelman D.G., Reed C.E., Nelson H.S., Offord K.P. (1993):
Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children.
Pediatrics; 92: 64-77.

Tinkelman D.G., Silk H.J. (1989):
Clinical and bacteriologic features of chronic sinusitis in children.
Am. J. Dis. Child.; 143: 938-942.

Toogood J.H., Jennings B., Greenway R.W., Chuang L. (1980):
Candidiasis and dysphonia complicating beclomethasone treatment of asthma.
J. Allergy Clin. Immunol.; 65: 145-153.

Toogood J.H., Baskervilla J.C., Markov A.E., Hodsman A.B., Jennings B., Haddad R.G., Drost D. (1995):
Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma.
J. Allergy Clin. Immunol.; 96: 157-166.

Toogood J.H., Jennings B., Hodsman A.B., Baskerville J., Fraher L.J. (1991):
Effects of dose and dosing schedule of inhaled budesonide on bone turnover.
J. Allergy Clin. Immunol.; 88: 572-580.

Toogood J.H., Markov A.E., Baskerville J., Dyson C. (1993):
Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma.

J. Allergy Clin. Immunol.; 91: 571-579.

Townley R.G., McGeady S., Bewtra A. (1976):
The effect of beta-adrenergic blockade on bronchial sensitivity to acetyl-beta-methacholine in normal and allergic rhinitis subjects.
J. Allergy Clin. Immunol.; 57: 358-366.

Turner B.W., Cail W.S., Hendley J.O., Hayden F.G., Doyle W.J., Sorrentino J.V., Gwaltney J.M.Jr. (1992):
Physiologic abnormalities in the paranasal sinuses during experimental rhinovirus colds.
J. Allergy Clin. Immunol.; 90(3): 474-478.

Turpeinen M, Sorva R., Juntunen-Backman K. (1991):
Changes in carbohydrate and lipid metabolism in children with asthma inhaling budesonide.
J. Allergy Clin. Immunol.; 88: 384-389.

Twarog F.J. (1991):
Home monitoring of asthma with peak expiratory flow rates.
Ann. Allergy; 67: 457-460.

Uotila M., Ruoslahti E., Engvall E. (1981):
Two-side sandwich enzyme immunoassay with monoclonal antibodies to human alpha-fetoprotein.
J. Immunol. Methods; 42 (1): 11-15.

VanAsperen P., Mellis C.M. (1981):
Bronchial reactivity in cystic fibrosis with normal pulmonary function.
Am. J. Dis. Child.; 135: 815-819.

Van Bever H.P., Stevens W.J. (1989):
Suppression of the late asthmatic reaction by hyposensitization in asthmatic children allergic to house-dust mites (Dermatophagoides pteronyssinus).
Clin. Exp. Allergy; 19: 399-404.

Vandenberg S.J., Heatley D.G. (1997):

Efficacy of adenoidectomy in relieving symptoms of chronic sinusitis in children.
Arch. Otolaryngol. Head Neck Surg.; 123 (7): 675-678.

van Essen-Zandvliet E.E., Hughs M.D., Waalkens H.J., Duiverman E.J., Pocock S.J., Kerrebijn K.F. (1992):
Effects of 22 months of treatment with inhaled corticosteroids and/or beta 2 -agonists on lung function, airway responsiveness, and symptoms in children with asthma.
Am. Rev. Respir. Dis.; 146: 547-554.

Varpela E., Laitinen L.A., Keskinen H., Korhola O. (1978):
Asthma, allergy and bronchial hyperreactivity to histamine in patients with bronchiectasis.
Clin. Allergy; 8: 273-280.

Vathenen A.S., Knox A.J., Wisniewski A., Tattersfield A.E. (1991):
Effect of inhaled budesonide on bronchial reactivity to histamine, exercise, and eucapnic dry air hyperventilation in patients with asthma.
Thorax; 46: 811-816.

Vedanthan P.R., Menon M.M., Bell T.D., Bergin D. (1977):
Aspirin and tartrazine in oral challenge: Incidence of adverse response in chronic childhood asthma.
J. Allergy Clin. Immunol.; 60: 8-13.

Venge P., Hakansson L. (1991):
The eosinophil and asthma. In:
Kaliner M.A., Barnes P.J., C.G.A. P. (eds.): Asthma Its Pathology and Treatment. New York, Marcel Dekker, Inc., pp. 477-502.

Verity C.M., VanHeule B., Carswell F., Hughes A.O. (1984):
Bronchial lability and skin reactivity in siblings of asthmatic children.
Arch. Dis. Child.; 59: 871-876.

Waalkens H.J., van Essen-Zandvliet E.E., Hughs M.D., Gerritsen J., Dwiverman E.J., Knol K., Kerrebijn (1993):

Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration.
Am. Rev. Respir. Dis.; 148: 1252-1257.

Wagenmann M., Naclerio R.M. (1992):
Anatomic and physiologic considerations in sinusitis.
J. Allergy Clin. Immunol.; 90 (3): 419-423.

Wald E.R. (1992):
Sinusitis in infants and children.
Ann. Otol. Rhinol. Laryngol.; 101: 37-41.

Wald E.R. (1992):
Microbiology of acute and chronic sinusitis in children.
J. Allergy Clin. Immunol.; 90 (3): 452-456.

Wald E.R. (1992):
Antimicrobial therapy of pediatric patients with sinusitis.
J. Allergy Clin. Immunol.; 90 (3): 469-473.

Wald E.R. (1998):
Microbiology of acute and chronic sinusitis in children and adults.
Am. J. Med. Sci.; 316 (1): 13-20.

Wald E.R., Byers C., Guerra N., Casselbrant M., Beste D. (1989):
Subacute sinusitis in children.
J. Pediatrics; 115 (1): 28-32.

Ware J., Dockery D., Spiro A., Speizer F.E., Ferris B.G. Jr. (1984):
Passive smoking, gas cooking and respiratory health of children living in six cities.
Am. Rev. Respir. Dis.; 129: 366-374.

Warner J.O., Gotz M., Landau L.I. (1989):
Management of asthma: A consensus statement.
Arch. Dis. Child.; 64:1065-1079.

Weille F.L. (1936):
Studies in asthma: Nose and throat in 500 cases of asthma.
N. Engl. J. Med.; 215: 235.

Weinberger M., Hendeles L. (1996):
Theophylline in asthma.
N. Engl. J. Med.; 334: 1380-1388.

Weiss K.B., Wagener D.K. (1990):
Changing patterns of asthma mortality identifying target populations at high risk.
JAMA; 264: 1683-1687.

Weiss S.T., Tager I.B., Speizer F.E., Rosner B. (1980):
Persistent wheeze. Its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children.
Am. Rev. Respir. Dis.; 122: 697-707.

Weller P.F. (1994):
Eosinophils: Stucture and functions.
Current opinion in Immunology; 6: 91-97.

White M.A., Kaliner M.A. (1991):
Mast cells and asthma. In:
Kaliner M.A., Barnes P.J., Persson C.G.A. (eds.): Asthma Its Pathology and Treatment.
New York, Marcel Dekker, Inc., pp. 409-440.

Williams H.E., McNichol K.N. (1969):
Prevalence, natural history and relationship of wheezing bronchitis to asthma in children.
BMJ; 4: 321-325.

Wilson N.M. (1989):
Wheezy bronchitis revisited.
Arch. Dis. Child.; 64: 1194-1199.

Wilson N.W., Jalowayski A.A. (1988):

A comparison of nasal cytology with sinus X-ray for the diagnosis of sinusitis.
Am. J. rhinol.; 2: 55-59.

Winther B., Gwaltney J.M. (1990):
Therapeutic approach to sinusitis with anti-infectious therapy as the baseline of management.
Otolaryngol. Head Neck Surg.; 103 (5): 876-879.

Witlig H., Bellot J., Fillippi I., Royal G. (1980):
J. Allergy Clin. Immunol.; 66: 305-309.

Wolf G., Greistorfer K., Jebeles J.A. (1995):
The endoscopic endonasal surgical technique in the treatment of chronic recurring sinusitis in children.
Rhinology; 33(2): 97-103.

Wolthers O.D. (1996):
Long-, intermediate- and short-term growth studies in asthmatic children treated with inhaled glucocorticoids.
Eur. Respir. J.; 9: 821-827.

Woods R.A., Chapman M.D., Adkinson F.N. Jr., Eagleston P.A. (1989):
The effect of cat removal on allergen content in household-dust samples.
J. Allergy Clin. Immunol.; 83: 730-734.

Woolcock A, Lunback B., Ringdal N., Jacques L.A. (1996):
Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroid.
Am. J. Respir. Crit. Care Med.; 153: 1481-1488.

Wong C.S., Cooper S., Britton J.R., Tattersfield A.E. (1993):
Steroid sparing effect of nedocromil sodium in asthmatic patients on high doses of inhaled steroids.
Clin. Exp. Allergy; 23: 370-376.

Wright A., Holberg C., Martinez F., Taussig. L.M. (1991):

Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illnesses in infancy.
J. Pediatr.; 118: 207.

Yan K., Salome C.M., Woolcock A.J. (1985):
Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease.
Am. Rev. Respir. Dis.; 132:25-29.

Yates D.H., Sussman H.S., Shaw M.J., Barnes P.J., Chung K.F. (1995):
Regular formoterol treatment in mild asthma. Effect on bronchial responsiveness during and after treatment.
Am. J. Respir. Crit. Care Med.; 152: 1170-1174.

Yonkers A.J. (1992):
Sinusitis- inspecting the causes and treatment.
Ear Nose Throat J.; 71(6): 258-262.

Young S., Le Souef P.N., Geelhoed G.C., Stick S.M., Turner K.J., Landau L.I. (1991):
The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy.
N. Engl. J. Med.; 324: 1168-1173.

Yunginger J.W., Reed C.E., O'Connell E.J., Melton L.J., O'Fallon W.M., Silverstein M.D. (1992):
A community-based study of the epidemiology of asthma: Incidence rates 1964-1983.
Am. Rev. Respir. Dis.; 146: 888-894.

Zedan M.M., Abdel Rahman H.A., Maamon N.M., Sheishaa A.A. and Abou Bakr H.M. (1990):
Risk and prognostic factors of bronchial asthma in children.
J. Bio. Med. Sci. Ther.; 6 (1): 26-40.

Zeiss C.R. (1992):
Intensive pharmacology.
Chest; 101: 407S-409S.

Ziment I. (1991):
Help for an overtaxed mucociliary system: managing abnormal mucus.
J. Respir. Dis.; 12: 21-33.

Ziment I, Stein M. (1993):
Inappropriate and unusual remedies. In:
Weiss E.B., Stein M, eds. Bronchial Asthma.
Boston: Little, Brown and Company, pp. 1145-1151.

Zimmerman B., Chambers C., Forsyth L. (1988):
Allergy in asthma. II. The highly atopic infant and chronic asthma.
J. Allergy Clin. Immunol.; 81: 71-76.

Zimmerman B., Feanny S., Reisman J., Hak H., Rashed N., Mclaughlin F.J., Levison H. (1988):
Allergy in asthma. I. The dose relationship of allergy to severity of childhood asthma.
J. Allergy Clin. Immunol.; 81: 63-70.

Zimmerman B., Gold M. (1991):
Role of sinusitis in asthma.
Pediatrician; 18: 312- 316.

Zinreich S.J. (1992):
Imaging of chronic sinusitis in adults. X-ray, computed tomography and magnetic resonance imaging.
J. Allergy Clin. Immunol.; 90 (3): 445-451.

APPENDIX

The SAS System 10:16 Sunday, January 23, 2000

GENDER	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	50	50.0	50	50.0
2	50	50.0	100	100.0

AGE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
7.0	12	12.0	12	12.0
7.5	3	3.0	15	15.0
8.0	12	12.0	27	27.0
8.5	5	5.0	32	32.0
9.0	17	17.0	49	49.0
9.5	6	6.0	55	55.0
10.0	10	10.0	65	65.0
11.0	10	10.0	75	75.0
11.5	2	2.0	77	77.0
12.0	7	7.0	84	84.0
12.5	3	3.0	87	87.0
13.0	2	2.0	89	89.0
13.5	2	2.0	91	91.0
14.0	6	6.0	97	97.0
15.0	3	3.0	100	100.0

ONSET	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1.0	3	3.0	3	3.0
1.5	5	5.0	8	8.0
2.0	9	9.0	17	17.0
2.5	8	8.0	25	25.0
3.0	10	10.0	35	35.0
3.5	3	3.0	38	38.0
4.0	4	4.0	42	42.0
4.5	4	4.0	46	46.0
5.0	8	8.0	54	54.0
5.5	3	3.0	57	57.0
6.0	10	10.0	67	67.0
6.5	1	1.0	68	68.0
7.0	9	9.0	77	77.0
7.5	3	3.0	80	80.0
8.0	8	8.0	88	88.0
8.5	1	1.0	89	89.0
9.0	3	3.0	92	92.0
10.0	1	1.0	93	93.0
11.0	5	5.0	98	98.0
12.0	2	2.0	100	100.0

The SAS System 10:16 Sunday, January 23, 2000

FOOD	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	84	84.0	84	84.0
1	16	16.0	100	100.0

DRUGS	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	86	86.0	86	86.0
1	14	14.0	100	100.0

ALLERGY	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	78	78.0	78	78.0
1	22	22.0	100	100.0

PRESENCE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	79	79.0	79	79.0
1	21	21.0	100	100.0

SMOKING	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	72	72.0	72	72.0
1	22	22.0	94	94.0
2	6	6.0	100	100.0

FH	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	73	73.0	73	73.0
1	27	27.0	100	100.0

The SAS System 10:16 Sunday, January 23, 2000

CONJUNC	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	83	83.0	83	83.0
1	17	17.0	100	100.0

SKIN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	68	68.0	68	68.0
1	32	32.0	100	100.0

RHINITIS	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	81	81.0	81	81.0
1	19	19.0	100	100.0

SINUSITI	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	69	69.0	69	69.0
1	14	14.0	83	83.0
2	17	17.0	100	100.0

RYEGRASS	Frequency	Percent	Cumulative Frequency	Cumulative Percent
2	1	50.0	1	50.0
3	1	50.0	2	100.0

Frequency Missing = 98

ASPER	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	2	16.7	2	16.7
2	4	33.3	6	50.0
3	2	16.7	8	66.7
4	4	33.3	12	100.0

Frequency Missing = 88

PENICIL	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1	9.1	1	9.1
2	6	54.5	7	63.6
3	2	18.2	9	81.8
4	2	18.2	11	100.0

Frequency Missing = 89

HOUSE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	9	31.0	9	31.0
2	9	31.0	18	62.1
3	6	20.7	24	82.8
4	5	17.2	29	100.0

Frequency Missing = 71

FEATHER	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	4	44.4	4	44.4
2	5	55.6	9	100.0

Frequency Missing = 91

WOOL	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	2	50.0	2	50.0
2	2	50.0	4	100.0

Frequency Missing = 96

The SAS System 10:16 Sunday, January 23, 2000

FLY	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1	100.0	1	100.0

Frequency Missing = 99

COCK	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1	33.3	1	33.3
2	1	33.3	2	66.7
3	1	33.3	3	100.0

Frequency Missing = 97

FARINA	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	2	28.6	2	28.6
2	2	28.6	4	57.1
3	1	14.3	5	71.4
4	2	28.6	7	100.0

Frequency Missing = 93

PTERON	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	2	28.6	2	28.6
2	3	42.9	5	71.4
3	1	14.3	6	85.7
4	1	14.3	7	100.0

Frequency Missing = 93

The SAS System 10:16 Sunday, January 23, 2000

PEFR	Frequency	Percent	Cumulative Frequency	Cumulative Percent
90	5	5.0	5	5.0
95	1	1.0	6	6.0
100	3	3.0	9	9.0
110	7	7.0	16	16.0
115	4	4.0	20	20.0
120	5	5.0	25	25.0
130	5	5.0	30	30.0
135	1	1.0	31	31.0
140	2	2.0	33	33.0
150	7	7.0	40	40.0

155	1	1.0	41	41.0
160	7	7.0	48	48.0
165	1	1.0	49	49.0
170	3	3.0	52	52.0
175	1	1.0	53	53.0
180	3	3.0	56	56.0
185	2	2.0	58	58.0
190	4	4.0	62	62.0
195	3	3.0	65	65.0
200	6	6.0	71	71.0
205	1	1.0	72	72.0
210	10	10.0	82	82.0
215	3	3.0	85	85.0
220	2	2.0	87	87.0
225	1	1.0	88	88.0
270	3	3.0	91	91.0
275	1	1.0	92	92.0
285	1	1.0	93	93.0
290	1	1.0	94	94.0
300	1	1.0	95	95.0
315	1	1.0	96	96.0
320	1	1.0	97	97.0
325	1	1.0	98	98.0
345	1	1.0	99	99.0
350	1	1.0	100	100.0

The SAS System 10:16 Sunday, January 23, 2000

PEFAT	Frequency	Percent	Cumulative Frequency	Cumulative Percent
130	3	3.0	3	3.0
140	3	3.0	6	6.0
150	1	1.0	7	7.0
160	9	9.0	16	16.0
165	3	3.0	19	19.0
170	5	5.0	24	24.0
180	2	2.0	26	26.0
190	2	2.0	28	28.0
200	8	8.0	36	36.0
210	8	8.0	44	44.0
220	4	4.0	48	48.0
225	2	2.0	50	50.0
230	5	5.0	55	55.0
235	1	1.0	56	56.0
240	8	8.0	64	64.0
245	4	4.0	68	68.0
250	2	2.0	70	70.0
260	5	5.0	75	75.0
265	2	2.0	77	77.0
270	5	5.0	82	82.0
275	2	2.0	84	84.0
280	2	2.0	86	86.0
300	1	1.0	87	87.0
310	1	1.0	88	88.0
320	1	1.0	89	89.0

325	1	1.0	90	90.0
330	1	1.0	91	91.0
340	1	1.0	92	92.0
350	2	2.0	94	94.0
375	1	1.0	95	95.0
390	1	1.0	96	96.0
400	1	1.0	97	97.0
410	1	1.0	98	98.0
430	1	1.0	99	99.0
440	1	1.0	100	100.0

CXRAY	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	64	64.0	64	64.0
1	36	36.0	100	100.0

XRAY	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	66	66.0	66	66.0
1	13	13.0	79	79.0
2	21	21.0	100	100.0

EOS1	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1	1.0	1	1.0
1	8	8.0	9	9.0
2	8	8.0	17	17.0
3	5	5.0	22	22.0
4	6	6.0	28	28.0
5	5	5.0	33	33.0
6	9	9.0	42	42.0
7	5	5.0	47	47.0
8	6	6.0	53	53.0
9	2	2.0	55	55.0
10	6	6.0	61	61.0
11	4	4.0	65	65.0
12	5	5.0	70	70.0
13	1	1.0	71	71.0
14	3	3.0	74	74.0
15	5	5.0	79	79.0
16	2	2.0	81	81.0
17	2	2.0	83	83.0
18	4	4.0	87	87.0
19	2	2.0	89	89.0
20	2	2.0	91	91.0

22	2	2.0	93	93.0
24	2	2.0	95	95.0
26	3	3.0	98	98.0
28	2	2.0	100	100.0

The SAS System 10:16 Sunday, January 23, 2000

IGE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
10	10	10.0	10	10.0
20	2	2.0	12	12.0
30	1	1.0	13	13.0
35	1	1.0	14	14.0
40	2	2.0	16	16.0
50	1	1.0	17	17.0
60	5	5.0	22	22.0
70	7	7.0	29	29.0
80	8	8.0	37	37.0
90	5	5.0	42	42.0
100	5	5.0	47	47.0
110	4	4.0	51	51.0
120	4	4.0	55	55.0
130	4	4.0	59	59.0
150	1	1.0	60	60.0
160	1	1.0	61	61.0
180	3	3.0	64	64.0
190	3	3.0	67	67.0
200	1	1.0	68	68.0
210	1	1.0	69	69.0
230	1	1.0	70	70.0
240	2	2.0	72	72.0
250	1	1.0	73	73.0
260	1	1.0	74	74.0
270	1	1.0	75	75.0
280	3	3.0	78	78.0
310	1	1.0	79	79.0
320	2	2.0	81	81.0
340	1	1.0	82	82.0
370	1	1.0	83	83.0
400	1	1.0	84	84.0
420	1	1.0	85	85.0
480	1	1.0	86	86.0
530	1	1.0	87	87.0
540	1	1.0	88	88.0
620	1	1.0	89	89.0
640	3	3.0	92	92.0
650	1	1.0	93	93.0
660	1	1.0	94	94.0
680	1	1.0	95	95.0
720	1	1.0	96	96.0
730	1	1.0	97	97.0
780	1	1.0	98	98.0
820	1	1.0	99	99.0
840	1	1.0	100	100.0

The SAS System 10:16 Sunday, January 23, 2000

GROUP	Frequency	Percent	Cumulative Frequency	Cumulative Percent
MILD	33	33.0	33	33.0
MOD	29	29.0	62	62.0
SEVERE	38	38.0	100	100.0

ARABIC SUMMARY

الملخص العربى

الربو الشعبى من الأمراض الأكثر شيوعا بين الأطفال وهو مسئول عن نسبة كبيرة من أيام الغياب عن المدرسة بسبب المرض المزمن.

الربو الشعبى يوجد على رأس قائمة الأسباب المؤدية لدخول المستشفيات بالنسبة للأطفال. ويمكن اعتبار أن الربو الشعبى مرض انسدادى عام بالرئة ويصاحبه: ١- انسداد بالقصبات الهوائية وهو انعكاسى (ليس بالدرجة الكاملة فى بعض المرضى) تلقائيا أو بتأثير العلاج. ٢- التهاب القصبات الهوائية. ٣- ازدياد رد فعل القصبات الهوائية للعديد من المهيجات.

ويوجد نوعان من الربو الشعبى وهما الخارجى أو التحسسى وفيه تحدث نوبات المرض عقب التعرض لعوامل بيئية مثل الغبار وحبوب اللقاح وعادة ما يصاحب ذلك ازدياد فى نسبة أجسام المناعة (E) فى المصل عند المرضى المصابين بهذا النوع، والنوع الآخر هو الربو الداخلى الذى لا يختلف عن النوع الأول اكلينيكيا، ولكن لا تحدث فيه زيادة فى نسبة أجسام المناعة (E) فى المصل ويكون اختبار حساسية الجلد فيه سالبا.

وقد أثبتت الدراسات المختلفة بالخارج وجود علاقة بين التهاب الجيوب الأنفية ومرضى الربو الشعبى فى الأطفال، حيث يحدث التهاب الجيوب الأنفية عند أطفال الربو الشعبى أكثر من الأطفال الطبيعيين وكذلك تزداد حدة الربو الشعبى عندما يصاحبه التهاب بالجيوب الأنفية.

وفى هذه الدراسة تم اختيار مائة طفل مصرى مصاب بمرض الربو الشعبى، تتراوح أعمارهم بين ٧ و ١٥سنة (٥٠ من الذكور و ٥٠ من الاناث) وهم على درجات متفاوتة من حدة الربو الشعبى وقد تم اختيارهم من بين المرضى المترددين على قسم الأطفال بمستشفى المطرية التعايمى (العيادة الخارجية و القسم الداخلى) خلال الفترة من أول يناير ١٩٩٥م وحتى آخر ابريل ١٩٩٦م. وقد تم أخذ تاريخهم المرضى وفحصهم اكلينيكيا بالكامل واجراء قياس لأعلى معدل لتيار الزفير (P.E.F.R.) واجراء اختبار حساسية الجلد وتحديد مستوى أجسام المناعة (E) فى المصل بطريقة ال E.L.I.S.A. وصورة دم كاملة وفحص بأشعة اكس للصدر والجيوب الأنفية وقد تم ذلك لجميع المرضى الذين خضعوا للدراسة.

وبتحليل بيانات ونتائج البحث تم تقسيم المائة مريض الى ثلاث مجموعات حسب حدة الربو الشعبى بينهم كالأتى :

مجموعة ربو شعبى بسيط، مجموعة ربو شعبى متوسط الشدة و مجموعة ربو شعبى شديد.

وقد أوضحت النتائج الآتى:-

– أن هناك تدرجا فى نسبة انخفاض أعلى معدل لتيار الزفير (P.E.F.R.) من مجموعة الربو الشعبى البسيط الى مجوعة الربو الشعبى متوسط الشدة الى مجموعة الربو الشعبى الشديد.

– أن هناك تدرجا فى نسبة ارتفاع الeosinophils فى الدم وفى نسبة ارتفاع الأجسام المضادة (E) فى المصل من مجموعة الربو الشعبى البسيط الى مجموعة الربو الشعبى متوسط الشدة الى مجموعة الربو الشعبى الشديد.

لم تثبت النتائج أن هناك علاقة بين السن عند بداية مرض الربو الشعبى وبين وجود التهاب بالجيوب الأنفية، وان كان هناك دلالة احصائية على أن السن عند بداية المرض كان أصغر فى مجموعة الربو الشعبى البسيط بالمقارنة بمجموعتى الربو الشعبى متوسط الشدة والربو الشعبى الشديد.

كذلك أثبتت النتائج احصائيا أن مجموعة الربو الشعبى الشديد ارتبطت بمعدل أكبر من حساسية الأنف ووجود ظواهر مرضية للربو الشعبى بأشعة أكس للصدر ودلائل ايجابية على وجود التهاب بالجيوب الأنفية بأشعة اكس للجيوب الأنفية.

وقد أثبتت النتائج أن ٣٤% من المرضى الذين تمت دراستهم يعانون من التهاب الجيوب الأنفية وهى نسبة تقارب بعض النسب الموجودة بالدراسات التى تمت بالخارج، وكذلك وجد أن من بين هؤلآء كانت نسبة الربو الشعبى الشديد بينهم تبلغ ٥٤.٨ % وهى نسبة ذات دلالة احصائية، وكذلك لوحظ وجود دلالات احصائية بين وجود التهاب بالجيوب الأنفية ووجود تاريخ مرضى للحساسية بين افراد اسرة المريض، ووجود حساسية بالأنف عند المريض، وايجابية اختبار حساسية الجلد وارتفاع أكبر لنسبة الeosinophils فى الدم وارتفاع أكبر لنسبة أجسام المناعة (E) بالمصل .

وبذلك تكون هذه الدراسة قد أثبتت وجود علاقة بين حدوث التهاب بالجيوب الأنفية ودرجة شدة الربو الشعبى عند الأطفال المصريين الذين تمت دراستهم وأيضا أن زيادة معدل وجود التهاب بالجيوب الأنفية مرتبط بالربو الشعبى الخارجى أو التحسسى أكثر من الربو الشعبى الداخلى.

وعلى ضؤ هذه الدراسة، فانه ينصح بالبحث عن التهاب الجيوب الأنفية وعلاجه عند الأطفال المصابين بالربو الشعبى وخاصة النوع الشديد أو الخارجى منه بهدف تخفيف شدة هذا الربو الشعبى.

المستخلص العربى

التهاب الجيوب الانفية عند الاطفال المصابين بالربو الشعبى وعلاقة ذلك بشدة ونوع الربو الشعبى

الجندى م.ع.س.، ضيف م.ك.د.، خلاف إ.ى.، فودة أ.م.ر.

مائة من الأطفال المصريين المصابين بالربو الشعبى تم أدراجهم فى الدراسة من بين المرضى المترددين على قسم طب الأطفال بمستشفى المطرية التعليمى بالقاهرة (٥٠ من الذكور و ٥٠ من الإناث). وقد تم عمل الآتى لهم جميعا: اخذ التاريخ المرضى لهم، فحصهم اكلينيكيا بالكامل، قياس أعلى معدل للزفير (P.E.F.R.)، اختبار حساسية الجلد، تحديد مستوى الاجسام المضادة E فى المصل بطريقة الـ E.L.I.S.A.، صورة دم كاملة، اشعة اكس للصدر وللجيوب الانفية. حسب النتائج تم تقسيم المرضى الى ثلاث مجموعات: مجموعة الربو الشعبى البسيط (٣٣ مريض)، مجموعة الربو الشعبى المتوسط الشدة (٢٩مريض) مجموعة الربو الشعبى الشديد (٢٨ مريض).

الدراسة اثبتت وجود علاقة بين حدوث التهاب بالجيوب الانفية ودرجة شدة الربو الشعبى بين الاطفال المصريين الذين تمت دراستهم. وأن بين الاطفال المصابين بالتهاب الجيوب الانفية ٥٤,٨% يعانون من ربو شعبى شديد، ٢٥,٨% يعانون من ربو شعبى متوسط الشدة و١٩,٤% فقط يعانون من ربو شعبى بسيط (P = 0.049). الدراسة اثبتت ايضا مدى انتشار للربو الشعبى الخارجى بدرجة اعلى من الربو الشعبى الداخلى بين المرضى المصابين بالتهاب الجيوب الانفية (P = 0.01).

الكلمات المفتاحية :

الربو الشعبى عند الاطفال، التهاب الجيوب الانفية، أعلى معدل للزفير (P.E.F.R.)، اختبار حساسية الجلد، تحديد نسبة الاجسام المضادةE بالمصل بطريقة الـ E.L.I.S.A.

"جامعة عين شمس"
الكلية: معهد الدراسات العليا للطفولة

شكـــــر

اشكـــر الســـادة الأســـاتذة الـــذين قاموا بالاشـــ

وهـــم :

١) .....
٢) .....
٣) .....
٤) .....

ثم الأشخـــاص الذيـــن تعـــاونوا معـــى فـــى البحـــث

وهـــم :

١) .....
٢) .....
٣) .....

وكـــذلك الهيئـــات الأتيـــة :

١) .....
٢) .....
٣) .....

جامعة عين شمس

الكليـــة :

رسالـــة ~~ماجســــتير~~ / دكتـــــوراه

أسم الطـــالب: د/ أحمد محمد رشاد فوده ....

عنوان الرسالة: التهاب الجيوب الأنفية عند الأطفال المصابين بالربو الشعبي وعلاقة ذلك بشدة ونوع الربو الشعبي

أســم الدرجـــة : (~~ماجستيـــــر~~ / دكتـــــوراه)

لجنـــة الإشـــراف

١- الاسم/ أ.د. محمد عبد السلام الجندي ٢ الوظيفة/ أستاذ طب الأطفال - معهد الكبد - جامعة المنوفية

٢- الاسم/ أ.م.د. محمد حمدي إبراهيم حنفي ٢ الوظيفة/ أستاذ مساعد بقسم الدراسات الطبية - معهد الدراسات العليا للطفولة

٣- الاسم/ د. أ. سعاد يوسف خلاف ٢ الوظيفة/ استشاري ورئيس قسم الأطفال م. المطرية التعليمي

تاريخ البحـــث : ٢١ / ٢ / ١٩٩٤

الدراســـات العليـــا

ختـــم الإجـــازة :

/ ١٩٩

أجيزت الرسالـــة بتاريخ ٢٢/ ٧ / ٢٠٠٠

موافقة مجلس ~~الكلية~~ المعهد

٢/ ٧/ ٢٠٠٠

موافقة مجلس الجامعة

/ / ١٩٩

"جامعة عين شمس"
الكليـــة:

صفحـــة العنـــوان

أســـم الطالـــب : د/ أحمد محمد بشار فودة
الدرجـــة العلميـــة : دكتوراة الفلسفة في دراسات الطفولة
القسم التابع لـــــه : الدراسات الطبية
أســـم الكليـــة : معهد الدراسات العليا للطفولة
الجامعـــــــة : جامعة عين شمس
سنـــة التخـــرج :
سنـــة المنـــح : ٢٠٢٢

شـــروط عامـــة

يوضع شعـار الجامعـة علـى الغـلاف الخارجـي

بسم الله الرحمن الرحيم

وما أوتيتم من العلم الا قليلا

صدق الله العظيم

جـــامعة عين شـــمس
معهد الدراسات العليا للطفولة
قسم الدراسات الطبية

التهاب الجيوب الأنفية عند الأطفال المصابين بالربو الشعبى وعلاقة ذلك بشدة ونوع الربو الشعبى

بحث مقدم توطئة للحصول على درجة دكتوراة الفلسفة فى دراسات الطفولة
من معهد الدراسات العليا للطفولة – قسم الدراسات الطبية
جامعة عين شمس

مقدم من
الطبيب/ أحمد محمد رشاد فودة
ماجستير طب الأطفال – جامعة القاهرة

تحت اشراف

أ.د./ محمد عبد السلام الجندى
أستاذ طب الأطفال
معهد الكبد
جامعة المنوفية

أ.م.د./ مجدي كرم الدين ضيف
أستاذ مساعد بقسم الدراسات الطبية
معهد الدراسات العليا للطفولة
جامعة عين شمس

د./ اسعاد يوسف خلاف
استشارى ورئيس قسم الأطفال
مستشفى المطرية التعاونى

٢٠٠٠