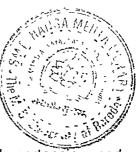
**RISK FACTOR ANALYSIS IN THE** 

# DEVELOPMENT OF CHRONIC

SUMMARY OF PhD THESIS SUBMITTED BY Ms. Swati A Desai October 2003

DEPARTMENT OF FOODS AND NUTRITION & WHO COLLABORATING CENTRE FOR ANAEMIA CONTROL & DIET RELATED NON COMMUNICABLE DISEASES FACULTY OF HOME SCIENCE M. S. UNIVERSITY OF BARODA VADODARA-390002, GUJARAT

## **SUMMARY**



Chronic degenerative diseases such as obesity, diabetes, hypertension, and chronic heart diseases are increasing to epidemic proportions and gaining their hold over the developing countries. Over the last two decades, the gratifying gain in cardiovascular health that occurred in the developed countries have been accompanied by an alarming escalation in the other and more populous regions of the world. In fact the World Health Organisation has warned of an epidemic of heart disease in developing countries over the next decade. While sharp demographic and lifestyle shift were brought about by recent urbanization and industrialization, globalization, which constituted the tail end of the twentieth century, accelerated the propulsion of the developing countries into the vortex of the global cardiovascular disease epidemic. Thus, globalization brings about not only changes in the prosperity of these countries but also ill health.

In fact, in India, post independence has witnessed a change in the dietary habits (more consumption of fatty foods) and an increase in the sedentary life style of the people. Thus, urbanization and industrialization along with these lifestyle changes has in turn resulted in escalating the prevalence of chronic degenerative diseases. The increasing prevalence of these diseases portray that the morbidity of these is on the rise, thus laying emphasis to study the risk factors associated with the same The present study was thus planned with an objective to map the prevalence and to study the risk factors for the development of chronic degenerative diseases in an industrial set up in Vadodara.

Of the 1025 subjects enrolled from the Indian Oil Corporation (Gujarat Refinery), Vadodara, 63.1% were males and 36.9% were females. The average age of the subjects was found to be 42 years. The average body mass index was found to be 24.7. The educational profile of the subjects revealed 29% of the subjects to be diploma holders or graduates. Majority of the subjects (78.6%) had per capita income greater than 1000, indicating that they were above the economically disadvantaged category.

There were two canteens that supplied food to the employees at highly subsidized rate. The average nutritive value of the snack packets provided by the canteen was 291 Kcal, and the protein, fat and carbohydrate content was found to be 8.3g, 23.2g and 18.4g respectively, implying that they were rich sources of calories and fat. Furthermore, the data revealed that the average monthly sale of snack packets irrespective of the food items was found to be very high, indicating the increased consumption of energy dense snacks from the canteen. This is also evident from the dietary analysis, which reveals the fat energy ratio of the subjects to be greater than 30%

In the present study the prevalence of chronic degenerative diseases such as overweight, obesity, diabetes, hypertension and chronic heart disease\_was found to be 33%, 8%, 8%, 6% and 1% respectively.

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The assessment of lipid levels of male and female subjects showed that the males had significantly raised levels of total cholesterol (TC), triglyceride (TG), very low density lipoprotein cholesterol (VLDL-C) and Non high density lipoprotein cholesterol (Non HDL-C) respectively. The impact of age on the lipid parameters of the subjects showed that those who were above the age of 40 years had significantly higher levels of TC, TG, LDL-C, VLDL-C and Non HDL-C in comparison to those below the age of 40 years.

In the present study the relative risk of diseased subjects to develop complications with respect to smoking, tobacco chewing and alcohol consumption was found to be 1.6, 1.3 and 1.4 respectively. These results thus indicate that the general habits of the subjects such as smoking, tobacco chewing and consumption of alcohol do play a role in worsening the metabolic profile of the subjects

The comparison of lipid levels among the normal and diseased subjects showed atherogenic dyslipidemia to be present in subjects suffering from various chronic degenerative diseases such as overweight & obesity, diabetes, hypertension and coronary heart disease respectively

Obesity as mentioned earlier is associated with detrimental changes in the lipid profile. In the present study significant rise in the atherogenic lipid levels was noticed with an increase in the body mass index of the subjects who were not suffering from any other chronic degenerative disease. This once again emphasizes the fact that overweight and obesity do carry a penalty for the



occurance of atherogenic dyslipidemia, which in turn is a risk factor chronic degenerative diseases

It is not only the amount of weight that one is carrying that is important, but the pattern of fat distribution is also important. Abdominal or android fat distribution in the central or upper body - has been found to be more risky for health than gluteal femoral or lower body or gynoid obesity. The correlation coefficient 'r' was 0 88 and 0.77 among male and female subjects when body mass index and waist circumference were compared, whereas the correlation coefficient 'r' was 0.4 and 0.02 among the male and female subjects when body mass index and waist hip ratio were taken into account. Thus emphasizing that body mass index and waist circumference are good indicators of body fat rather than using body mass index and waist hip ratio

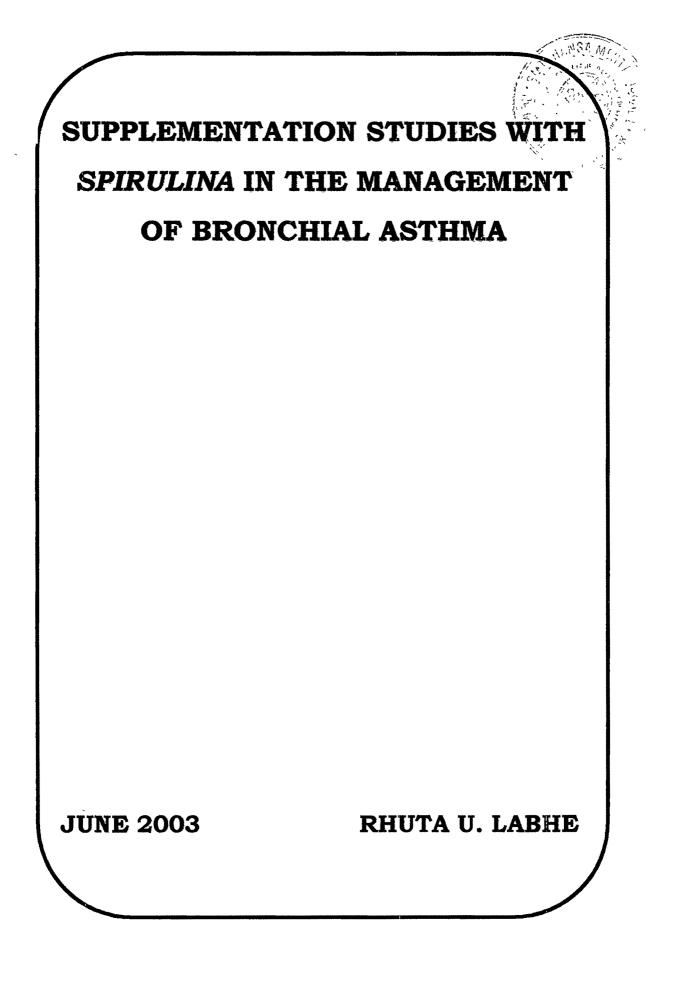
In addition to the comparison of lipid profile between various groups with respect to their disease profile, the analysis of relative risk of the subjects (Normals Vs Diseased) in relation to the lipid profile was also done so as to study the risk of various atherogenic lipid parameters. It was observed that among the overweight, obese, hypertensive and CHD subjects, TC was found to be the highly dependable risk factor in comparison to other lipid parameters whereas, among the diabetics TG (RR=4.4) was the more dependable risk factor followed by TC, LDL-C and Non HDL-C respectively

The ratios of Apo A1 / Apo B showed a decreasing trend among the dyslipidemic, overweight & obese, diabetic and hypertensive subjects thus

indicating their being at a greater risk of developing cardiovascular disease as the ratio is considered to be a sensitive index for predicting the risk.

The evidence that antioxidants may play a role in the prevalence of atherogeneis has been increasing rapidly in recent years. In the present study, the total antioxidant activity of the normal subjects was significantly higher than the overweight & obese, diabetic and hypertensive subjects. These results strengthen the fact that low levels of antioxidants may play a role in the development of ischemic heart disease.

Thus, from the results of the present study it can be summarized and concluded that the energy dense foods provided by the industrial canteens at highly subsidized rates would have been the plausible cause of increased prevalence of obesity along with sedentary lifestyle in this study population. Obesity, in turn, is emerging as the root cause of all the complications, thus it is aptly said to be the mother of chronic degenerative diseases. Moreover, the general habits of the people such as cigarette smoking, tobacco chewing and alcohol consumption do have a role to play in worsening the metabolic profile of the individuals. The study also portrays atherogenic dyslipidemia to be the hallmark of all these chronic degenerative diseases. Furthermore, the apolipoproteins and the total antioxidant activity which showed an adverse trend in the subjects suffering from various chronic degenerative diseases suggests their use as an additional tool for mapping the risk of cardiovascular disease This study thus highlights, that a more comprehensive approach is essential for effective prevention and/or management of chronic degenerative diseases.



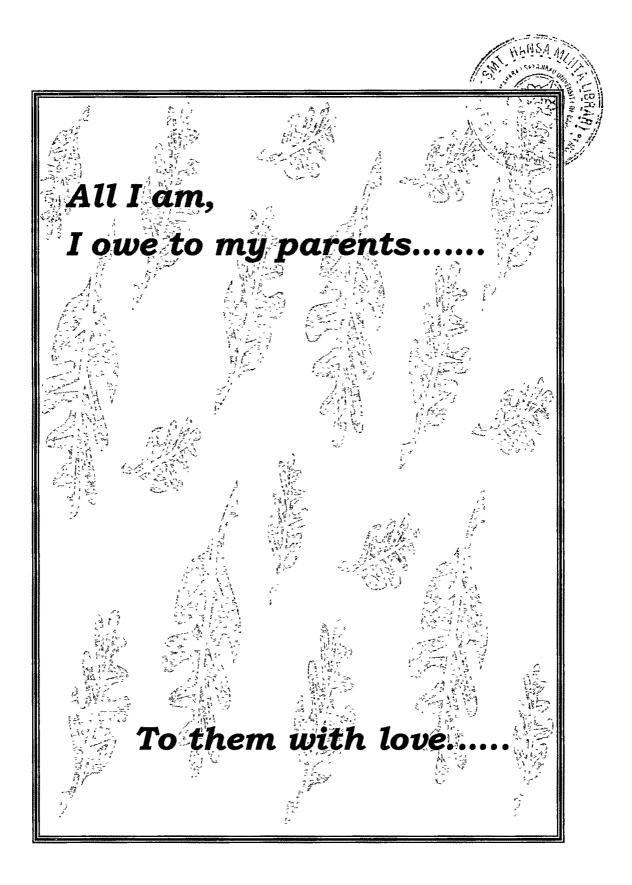
## SUPPLEMENTATION STUDIES WITH SPIRULINA IN THE MANAGEMENT OF BRONCHIAL ASTHMA

A Thesis Submitted To The Maharaja Sayajirao University Of Baroda For The Degree Of Doctor Of Philosophy

by

Rhuta U. Labhe

DEPARTMENT OF FOODS AND NUTRITION & WHO COLLABORATING CENTRE FACULTY OF HOME SCIENCE M. S. UNIVERSITY OF BARODA VADODARA-390002, GUJARAT June 2003



## DECLARATION



The author declares that this work has been carried out by her under the supervision of Prof. Uliyar V. Mani, Head, Department of Foods & Nutrition, Faculty of Home Science, M. S. University of Baroda and this work has not been submitted for any degree or diploma of any other university.

Rhula Labhe Rhuta U. Labhe

Prof. Uliyar V. Mani Guide & Supervisor

## CERTIFICATE



This is to certify that the thesis entitled "Supplementation" Studies With Spirulina In The Management of Bronchial Asthma" is based on the results of the work carried out by Ms. Rhuta U. Labhe for the PhD degree under my supervision and guidance. This work has not been submitted to any degree or diploma of any other university.

Prof. Uliyar V. Mani Guide & Supervisor

Date: 1<sup>g</sup> th June, 2003

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## LIST OF ABBREVIATIONS

AA	Arachidonic acid
A/G	Albumin /globulin
AEC	Absolute eosinophil count
BAL	Bronchoalveolar lavage
BCG	Bromocresol green
BMI	Body Mass Index
CO <sub>2</sub>	Carbon-dioxide
DC	Differential count
DGLA	Dihomo-gamma linolenic acid
DHA	Docosahexaenoic acid
EFA	Essential fatty acid
EPA	Eicosapentaenoic acid
FEV1	Forced Expiratory Volume in first second
FVC	Forced vital capacity
FEV1/FVC	Forced Expiratory Volume in first second/ Forced vital capacity
GLA	Gamma linolenic acid
GERD	Gastro-esophageal reflux disease
GSH-Px	Glutathione peroxidase
$H_2O_2$	Hydrogenperoxide
HHT	Hydroxy heptadecatrienoic acid
HPEPE	Hydroperoxy pentaenoic acid
HPETE	Hydroperoxy tetraenoic acid
IgE	Immunoglobulin E
IL	Interleukins
INF	Interferon
LTs	Leukotrienes
LTB <sub>4</sub>	Leukotriene B <sub>4</sub>
LTE5	Leukotriene E5
MDA	Malonaldialdehyde
NO <sub>2</sub>	Nitrogen dioxide



NSAIDs	Non steroidal anti-inflammatory drugs
<b>O</b> <sub>2</sub>	Oxygen
<b>O</b> <sub>3</sub>	Ozone
OR	Odds ratio
PAF	Platelet activating factor
PAR 2	Proteinase activated receptor-2
PEFR	Peak expiratory flow rate
PFT	Pulmonary function tests
PGs	Prostaglandins
PGD <sub>2</sub>	Prostaglandins D <sub>2</sub>
PGE <sub>1</sub>	Prostaglandin E <sub>1</sub>
PGE <sub>2</sub>	Prostaglandin E2
PGF <sub>2</sub> ¢	Prostaglandins $F_{2\infty}$
PGI <sub>2</sub>	Prostaglandins I <sub>2</sub>
PM	Particulate matter
PUFA	Polyunsaturated fatty acid
P/S	Polyunsaturates/saturates
RBG	Random blood glucose
ROS	Reactive Oxygen Species
RDA	Recommended daily allowance
SRS-A	Slow reacting substance of anaphylaxis
SO <sub>2</sub>	Sulphur di-oxide
SOD	Superoxide dismutase
Th	T-helper
Th1	Type 1 T-helper cells
Th2	Type 2 T-helper cells
ТС	Total Count
ТМВ	Tetra methyl benzidine
TXA <sub>2</sub>	Thromboxane A2
TXB <sub>2</sub>	Thromboxane B2
VIP	Vasoactive Intestinal Peptide
WHR	Waist-hip ratio

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#### Rhuta Labhe



Bronchial asthma is a disease of the airways that makes the airways prone to narrow too much and too easily in response to a wide variety of provoking stimuli. Its three major characteristics include airway obstruction, bronchial hyperresponsiveness and airway inflammation. In a quest of a non-medicinal, natural and nutritional care in the treatment of bronchial asthma; the present study was undertaken with an aim to assess the effectiveness of Spirulina supplementation in relieving bronchial obstruction in asthma patients. The thesis presents the results of the clinico-biochemical profile and pulmonary function status of asthma patients and the effect of spirulina supplementation on the protein status, IgE status and pulmonary function status of the asthma patients.

The thesis has been divided into six chapters.

**Chapter 1** gives a concise introduction of the topic along with the objectives of the study.

**Chapter 2** reviews elaborately the topic bronchial asthma by emphasizing on the recent literature available in this area.

Chapter 3 deals with the various methodologies employed in conducting the study.Chapter 4 presents the detailed findings of the study along with the discussion of the results under three sections:

Section I deals with the clinico-biochemical profile and pulmonary function status of asthma patients.

Section II presents the results of the effect of spirulina supplementation on the protein status and IgE status of the asthma patients.

Part of the present study has been published and communicated in the following journals/proceedings:

#### **Research Publications:**

- The effect of spirulina in the treatment of bronchial asthma. J Nutraceut Func Med Fds, 3(4): 53-61, 2001.
- Effect of functional food-Spirulina in the management of bronchial asthma. Ann Nutr Metabolism (1) pg: 107-108, 2001.
- Role of Spirulina in the management of bronchial asthma.
  Abstract book of IX Asian Congress of Nutrition, New Delhi, pg: 281, 2003.
- 4) Clinico-biochemical profile of asthmatics and its role in planning intervention strategies.
   Souvenir of the II International Symposium on Molecular Medicine, Vadodara, pg: 89, 2002.
- The therapeutic role of spirulina in the management of bronchial asthma. Scientific Programme & Abstracts, XXXII Annual Meeting of Nutrition Society of India, Coimbatore,pg:36, 1999.
- Metabolic alterations in bronchial asthma patients.
  Jr.Clin Biochem & Nutr (communicated)

#### **Chapter in Proceedings**

 Management of bronchial asthma with spirulina.
 Proc. of International symposium on recent advances in Molecular Biology, Allergy and Immunology, Ch: 14, pg: 138-143, 2000.







Bronchial asthma, a chronic inflammatory disorder, is one of the serious health problems affecting people worldwide. The chronically inflamed airways are hyperresponsive, become obstructed and the airflow is limited, when the airways are exposed to various stimuli or triggers. Asthma causes recurring episodes of coughing, wheezing, chest tightness and difficulty in breathing. The goal in the management of asthma today, has moved from symptomatic relief to long-term preventive treatment. It is here that emphasis needs to be laid on the efficacy of the asthmatic drugs in terms of prompt action and fewer to no side effects on longer use. Hence, alternative antiasthma therapies, which are specific for asthmatic inflammation and lack adverse effects need to be focused. Thus, in this direction the present study was conceived and planned with the objective to assess the effectiveness of Spirulina supplementation in relieving bronchial obstruction in asthma patients.

Seventy-eight patients suffering from mild to moderate degree of bronchial asthma were enrolled and their baseline data regarding nutritional status (anthropometric measurements and dietary history), socio-economic profile (name, age, education, occupation, family composition, per capita income), medical history, respiratory symptoms, triggering agents, medication details and general habits (smoking & alcohol consumption), pulmonary function tests (PFT) and biochemical parameters (random blood glucose, serum total protein and its fractions, serum IgE and haemogram profile) was collected. The asthma patients were further categorised into three groups:

**Group A:** the control group was kept only on medication for a period of four months, **Group B:** the experimental group was administered medication and spirulina (1g/day) for a period of two months after which the spirulina was withdrawn for the next two months and the medication was continued; and

**Group C:** also the experimental group, which was, administered only spirulina (1g/day) for period of four months.

The study was designed as a clinical intervention trial with drugs as control .The patient's in-group A and B were on bronchodilators and anti-inflammatory drugs and their medication was not altered during the intervention trial. The serum total protein, albumin and globulin, IgE levels were analysed and the pulmonary function tests were performed at the end of two and four months period.

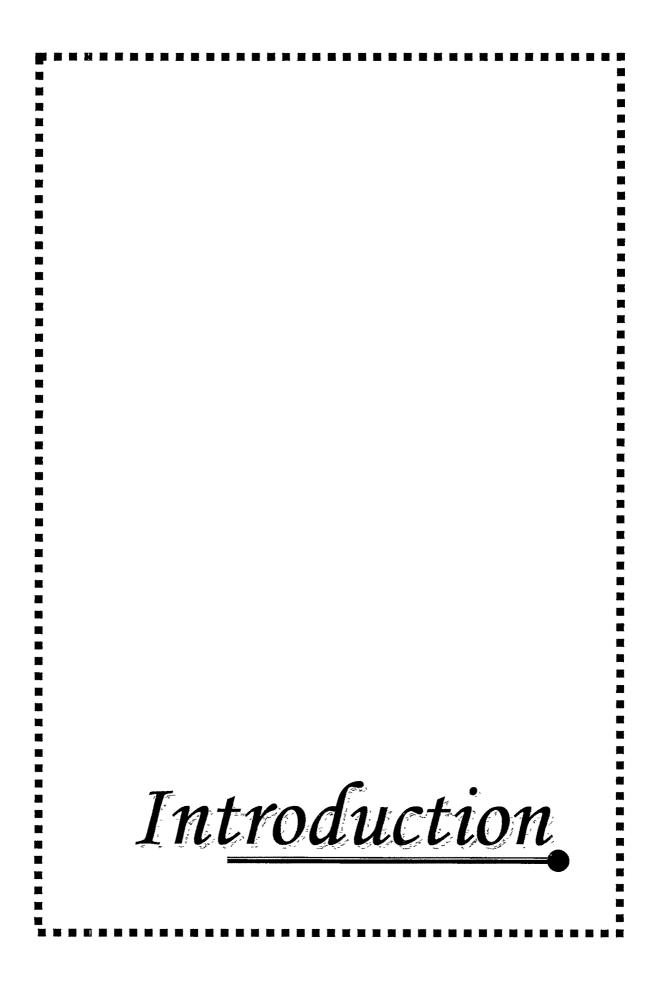
The mean age of asthma patients was found to be 40 years. The mean Body Mass Index (BMI) was found to be 20.50 in case of males and 22.94 in the case of females, which falls in the normal range. Dyspnoea or shortness of breath was the most common symptom experienced by majority of asthmatics (71%) and with regard to triggering agents, majority of the patients (83%) identified dust and fumes in the environment as a triggering agent in asthma attack. The biochemical profile of the asthmatics at baseline revealed that their protein status remained in the normal range. The mean serum IgE value was found to be  $405.22 \pm 2.88$  IU/ml in the asthmatics and it was observed that with increase in severity, longer duration of disease and smoking habits, the IgE levels tended to be higher. The pulmonary function status of the asthmatics revealed that the mean values of FVC, FEV1, FEV1/FVC and PEFR (% predicted) were found to be  $74 \pm 19$ ,  $64 \pm 14,81 \pm 18$  and  $48 \pm 19$  respectively and that with increase in severity, longer duration of disease and smoking habits, the values were found to be lowered.

On supplementation with spirulina , the results revealed that the total protein value remained unaltered in Group A (only medication) and it showed a slight nonsignificant increase in Group B (medication+ spirulina) after a period of four months. However, in Group C, which was on exclusive spirulina supplementation, a significant rise in total protein value was observed after a period of four months  $(6.46\pm0.72 \text{ to } 7.02\pm0.70 \text{ g/dl})$ . With regards the IgE status, in Group A (only medication) a non-significant increase in serum IgE values was observed over the four month period while in Group B (medication+ spirulina) the IgE value showed a significant decrease (277.58±3.89 to 275.5±3.24 IU/ml) in two months of spirulina supplementation. However, when the supplements were withdrawn in the next two months, a non-significant increase (275.5±3.24 to 304.71±2.88 IU/ml) in IgE level was observed. In Group C (only spirulina) patients who were on continued spirulina supplementation the IgE value showed a significant decrease over a period of four months (443.51±1.86 to 378.59±1.74 IU/ml).

The pulmonary function tests (PFT) namely, FVC, FEV1, PEFR and FEV1/FVC revealed an overall improvement in pulmonary function efficacy in all the three groups. Group A patients (only medication) showed a significant improvement in % FEV1 and % FEV1/FVC values over a period of four months. In patients of Group B all the four pulmonary function variables showed a significant improvement (% FVC-72±17 to  $83\pm17$ , % FEV1-61±14 to  $74\pm19$ , % PEFR-  $43\pm18$  to  $56\pm19$  and % FEV1/FVC-82±19 to  $88\pm15$ ) in the first two months of supplementation. However

when the supplements were withdrawn a significant reduction was observed in % FEV1 % FEV1/FVC and % FVC from two months to four months. In Group C patients who were on continued spirulina supplementation significant improvement was observed in % FVC, % FEV1 and % PEFR from baseline to four months.

Thus, a beneficial effect of spirulina was observed in improving the protein & IgE status and the pulmonary function status in the spirulina supplemented groups as against the medication group (Group A). Further, a decrease in the pulmonary function efficacy observed on withdrawal of spirulina (Group B), does suggest its important contributory role in improving the pulmonary function of asthmatics. Most optimal results in controlling asthma have been observed when spirulina was administered along with medication on daily continuous basis (Group B). Thus, it can be concluded that spirulina can be introduced along with medicine as a therapeutic and dietary supplement in the treatment of asthmatics and in long run this may not only help to control asthma but also reduce the need of drugs in its treatment.





Healthy lungs are essential for a healthy life. They work by taking oxygen  $(O_2)$ , from the air we breathe in and then exchange it for carbon-dioxide  $(CO_2)$ , a deadly waste product made by the cells of the body. Once this exchange has taken place, the  $CO_2$  is eliminated by breathing it out or exhaling.

Bronchial asthma is a disease that affects the lungs and airways that deliver air to the lungs. It is the most common respiratory disorder characterized by episodic intrathoracic airway obstruction, airway hyper responsiveness and airway inflammation (Shankar 1996).

#### **PREVALENCE OF ASTHMA**

Bronchial asthma is a serious problem around the world, yet it continues to be under diagnosed and under treated. The world's asthma hotbed is a small southern Atlantic island, Tristan da Cunha, where one of every three inhabitants has asthma. The high incidence of asthma on this island is undoubtedly due to inbreeding as three of the island's original fifteen settlers had asthma.

Majority of the studies into prevalence of asthma have been carried out since 1960s and although early studies in Europe and the North American continent demonstrated the figure of 1-2%, later work has shown that this is a gross underestimate and that 7-11% is more realistic (Clough & Holgate 1989). The prevalence of asthma has been increasing since the early 1980s for all age, sex and racial groups. The overall ageadjusted prevalence of asthma rose from 30.7 per 1000 population in 1980 to a twoyear average of 53.8 per 1000 in 1993-94, which represents an increase of 75% (National Heart Blood and Lung Institute, National Institute of Health 1999). The Midspan Family Study Survey of parents and offspring investigated the intergenerational 20-year trends in the prevalence of asthma. It reported that in never smokers, age and sex standardized, the prevalence of asthma was 3% in 1972-76, which increased to 8.2% in 1996 (Upton et al 2000).

The prevalence of asthma is also increasing among children. It is the leading cause, among all chronic childhood diseases, of absence from school. In children aged 6-11 years, the reported prevalence of asthma obtained from first National Health & Nutrition Examination Survey (NHANES I) conducted from 1971 to 1975 was 4.8%. In the second study-conducted from 1976 to 1980,the prevalence of asthma in the same age group increased to 7.6% (Gergen et al 1988). According to the National Health Interview Survey, National Centre for Health Statistics, the prevalence among children of age group 5 to 14 increased 74%, from 42.8 per 1000 in 1980 to an average of 74.4 per 1000 in 1993-94 (National Heart Blood and Lung Institute, National Institute of Health 1999).

In India too, the prevalence of asthma has increased markedly. In a study carried out in Mumbai, as a co-operating center of the European Community Respiratory Health Survey (ECRHS), the adult asthma prevalence was found to be 3.5% by physician diagnosis and 17% using a very broad definition including those with asymptomatic bronchial hyperreactivity (Chowgule et al 1998).

#### PRINCIPAL FORMS OF BRONCHIAL ASTHMA

It has long been recognized that the clinical pattern of asthma varies markedly among populations and on this basis two principal types or forms of asthma have been recognized.

#### **EXTRINSIC ASTHMA**

These groups of patients develop asthma at a young age, have a family history of atopic predisposition, may have other atopic manifestations (e.g. skin and nasal allergies) and have evidence of IgE-mediated responses and allergic "triggers" to some extent.

#### **INTRINSIC ASTHMA**

This usually develops later in life. These groups of patients have a negative family history of asthma or atopy and often have severe asthma that is difficult to treat (Nadel 1994).

#### SYMPTOMS OF ASTHMA

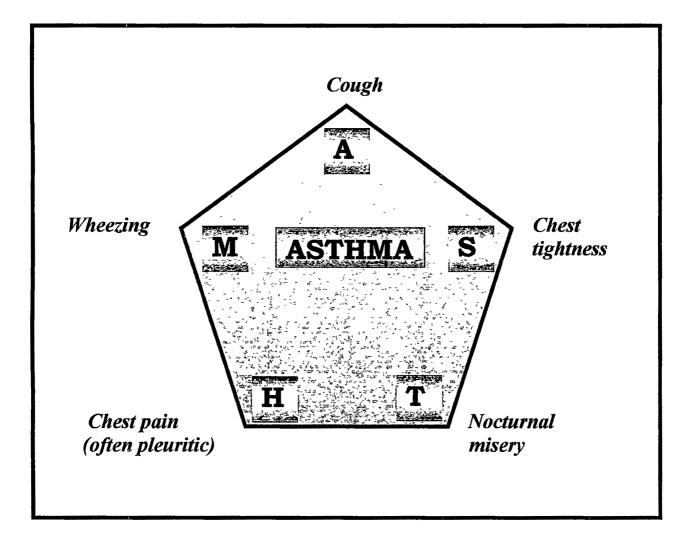
Characteristically patients with asthma have some combination of dyspnoea, wheeze, chest tightness and cough (Figure 1). The symptoms of asthma may vary from person to person and from time to time.

Dysphoea or shortness of breath, is a disturbance of breathing when in order to maintain a given level of ventilation, a disproportionate effort needs to be applied.

Wheeze is caused by turbulence in the air currents within the bronchi. Turbulence depends upon the reduction in airway caliber, which occurs in asthma, and the

### FIGURE 1

## SYMPTOMS OF ASTHMA



velocity of the airflow. Thus, the high velocity of flow through narrowed airways produces wheeze, which is often just as audible to the patient as to the physician.

A sensation of chest tightness and a feeling, that it is more difficult to breathe in than out are also the frequent complaints of many asthma patients.

Cough is a common feature of asthma. It may be dry, due to the stimulation of irritant receptors in the larger bronchi or it may be productive. Cough often develops as patients start to improve and the insipated mucus plugs that have occluded airway are dislodged into the tracheo-bronchial tree so that they can be expectorated. In addition, however cough may occur early and in fact, may be the only symptom in some patients.

One of the common features of asthma is the worsening of the symptoms at night. It is known that both normal people and asthmatic patients have a circadian rhythm of peak expiratory flow rate (PEFR). The PEFR is lowest between 3 and 6 a.m., as a result it is common for patients to wake in the early morning with symptoms of asthma (Pearson 1990, Williams Jr & Shim 1993).

#### **COMMON ASTHMA TRIGGERS**

In asthma, the narrowing of the airways occurs chiefly due to two reasons:

- The inside lining of the airways becomes red and swollen (inflammation) and there is hyper secretion of mucus.
- The muscles around the airways tighten (bronchoconstriction)

The above changes result when the airways are exposed to various stimuli, or triggers.

The common triggers, which precipitate the asthma symptoms of asthma, include:

#### INHALANT ALLERGENS

- Animal allergens, including dander, urine, faeces and saliva from any warm blooded animal, particularly cats, dogs, rabbits, mice and birds.
- House dust mites (common microscopic organism which thrives in areas of high humidity)
- Exposure to cockroach allergen
- Indoor fungi (molds), prominent in humid environment
- Outdoor allergens, particularly pollens from grass, weeds and trees

#### **INGESTED ALLERGENS**

Some foods (peanuts, eggs, dairy foods etc), food preservatives, flavourings, colourings etc.

#### IRRITANTS

- Smoke from tobacco or wood burning stoves
- Indoor / outdoor pollutants / chemicals including household sprays, volatile organic compounds such as polishes, cooking oils and industrial and photochemical smog

#### **OTHER FACTORS**

- ♦ Rhinitis/sinusitis
- Gastroesophageal reflux
- Sensitivity to Aspirin and other Non-Steroidal Anti Inflammatory Drugs (NSAIDs)
- Topical and systemic beta-blockers
- ◆ Viral respiratory infections, the bronchial epithelial damage and airway inflammation caused by viral infection can exacerbate asthma symptoms.
- Exercise
- Changes in temperature and weather
- Emotions

#### **ASTHMA CLASSIFICATION**

Based on the National Heart Blood and Lung Institute (NHBLI 1998) guidelines asthma can be classified into the following categories:

#### MILD INTERMITTENT ASTHMA

- Symptoms of cough, wheeze, chest tightness or difficulty breathing, less than twice a week
- Flare-ups-brief, but intensity may vary
- Night-time symptoms less than twice a month
- Lung function test FEV1 (Forced Expiratory Volume in first second) equal to or above 80 percent of normal values.

#### MILD PERSISTENT ASTHMA

- Symptoms of cough, wheeze, chest tightness or difficulty breathing, three to six times a week.
- ♦ Flare-ups-may affect activity level
- Night-time symptoms three to four times a month
- Lung function test FEV1 above 60 percent but below 80 percent of normal values.

#### **MODERATE PERSISTENT ASTHMA**

- Symptoms of cough, wheeze, chest tightness or difficulty breathing, daily
- ♦ Flare-ups-may affect activity level
- Night-time symptoms 5 or more times a month
- Lung function test FEV1 above 40 percent but below 60 percent of normal values.

#### SEVERE PERSISTENT ASTHMA

- Symptoms of cough, wheeze, chest tightness or difficulty breathing, continual
- Night-time symptoms frequently
- Lung function test FEV1 less than or equal to 40 percent of normal values

#### **ASTHMA: AN INFLAMMATORY DISEASE**

In the past few recent years, views about asthma have changed rather strikingly. Earlier, asthma was viewed simply as allergen-induced mast cell degranulation, resulting in the release of mediators such as histamine and slow reacting substance of anaphylaxis (SRS-A) that contracted airway smooth muscle. It has now become clear that asthma is a chronic inflammatory disease involving many interacting cells which release a whole variety of inflammatory mediators that activate several target cells in the airway, resulting in bronchoconstriction, microvascular leakage and oedema, mucus hypersecretion and stimulation of neural reflexes.

Inflammatory responses are concerned with defense against invasion by outside organism and with tissue repair, and are thus beneficial. However in asthma the inflammatory response appears to have been mounted inappropriately, leading to adverse effects. Inflammation is a general process, but the type of inflammatory response may vary considerably from tissue to tissue and with different initiating stimuli. The cardinal signs of inflammation are calor and rubor (heat and redness from vasodilation), tumour (swelling from plasma exudation and oedema) and dolor (pain from sensitization of sensory nerves). The cardinal signs of inflammation reflect the three major events of an inflammatory response:

- Vasodilation: An increase in the diameter of blood vessels-of nearby capillaries occurs as the vessels that carry blood away from the affected area constrict, resulting in engorgement of the capillary network. The engorged capillaries are responsible for redness and an increase in tissue temperature.
- Oedema: An increase in capillary permeability facilitates an influx of fluid and cells from the engorged capillaries into the tissue. The fluid that accumulates (exudate) has a much higher protein content than fluid normally released from the vasculature. Accumulation of exudate contributes to tissue swelling (oedema).
- Chemotaxis: Influx of phagocytes from the capillaries into the tissues is facilitated by the increase capillary permeability. The emigration of phagocytes is a complex series of events, including adherence of the cells to endothelial wall of the blood vessels (margination), followed by their emigration between the capillary-endothelial cells into the tissue (diapedesis or extravasation), and finally their migration through the tissue to the site of inflammatory response (chemotaxis). As phagocytic cells accumulate at the site and begin to phagocytose bacteria, they release lytic enzymes, which can damage the nearby healthy cells (Goldsby et al 1999).

Research into the disease has highlighted the importance of migration of inflammatory cells from circulation into the airway tissues and has emphasized the fact that the inflammatory process in asthmatic airways appears to have common features from patient to patient, irrespective of whether the asthma is allergic in origin or apparently non- allergic. Thus, although there may be several ways of initiating this inflammatory response, the inflammation that is characterized of asthma is typified by infiltration with eosinophils and lymphocytes and by shedding of airway epithelial cells. These inflammatory changes may be seen even in patients with the mildest of asthma (Barnes 1993).

The inflammation consists of many interacting cells such as eosinophils, neutrophils, macrophages, lymphocytes, activated mast cells along with oedema, vascular dilation, muscular gland proliferation and ultimately, sub-epithelial fibrosis all resulting from an array of chemical mediators (Menon 1997, Morris 1996). Each of the inflammatory cells has an important contribution and a specific relation to the development of airway inflammation and airway narrowing.

The mast cell has long been considered to be of paramount importance in the pathophysiology of asthma. Activation of mast cells by specific antigens through cellbound IgE releases histamine and causes synthesis of cysteinyl leukotrienes. These acute-phase mediators cause airflow obstruction by directly increasing airway smooth muscle tone. Mast cells also release proteases, pro-inflammatory cytokines and chemokines, which contribute to airway inflammation and airway hyper responsiveness (Shimizu & Schwartz 1997).

Eosinophils are considered to be one of the major cells that mediate much of the pathology and disordered airway function that characterizes asthma. Upon activation, these cells release several toxic mediators, reactive oxygen and leukotrienes as well as several pro-inflammatory cytokines, all of which contribute to increase airway hyper responsiveness and damage to the airway epithelium.

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T-lymphocytes, through their capacity to recognize foreign proteins processed by antigen-presenting cells, generate a wide range of cytokines relevant to asthma pathogenesis and play a central role in the initiation and persistence of the inflammatory response.

Macrophages also contribute to asthma pathogenesis by secreting a range of inflammatory mediators, including cytokines, chemokines and leukotrienes (Salvi 2001).

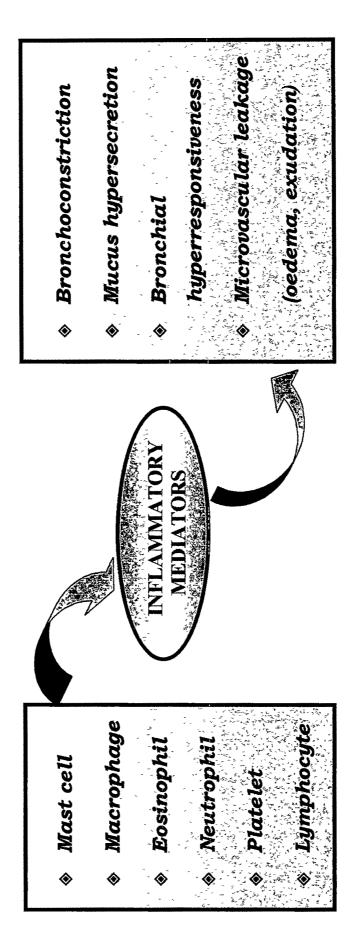
Thus, essentially, the mediators released from a variety of inflammatory cells in asthma, make up a "soup" of variable composition, which then leads to the characteristic triad of pathological features; viz;

- Contraction of bronchial and bronchiolar smooth muscle, which leads to a rapid increase in airflow resistance within the bronchi and bronchioles (bronchoconstriction)
- Solution Increased secretion of bronchial mucus (mucus hypersecretion)
- Solution Oedema of bronchial mucosa caused due to increased vascular permeability

Associated with all the three features is bronchial hyperreactivity or bronchial hyper responsiveness, the hallmark of asthma, which is as a result of a persistent inflammatory process in the bronchial mucosa and sub mucosa (Figure 2).

## FIGURE 2

# **ROLE OF INFLAMMATORY MEDIATORS IN ASTHMA**



## **MANAGEMENT OF ASTHMA**

Asthma attacks are episodic, but airway inflammation is chronically present, thus controlling an asthmatic disorder requires long-term management. The primary aim in management is to maintain the patient symptom free and to prevent long-term risks of the disease. Primarily, the management of asthma involves three basic principles:

- Avoidance of factors known to precipitate asthma or treatment of its cause (etiological treatment)
- Treatment of the attack itself and preventing the occurrence of further asthmatic attack
- Treatment of worsening and life threatening acute severe asthma attacks

Thus, the goals in asthma management include:

- Relieve symptoms and stop attacks
- Prevent long-term risks
- Restore normal airway function
- Require little or no quick relief medication
- Avoid side effects of drugs

## **ASTHMA MEDICATIONS**

In asthma, the airways of the lungs are narrowed as a result of spasm of airway muscles (bronchospasm), infiltration of airway lining by inflammatory cells and accumulation of secretions in the lumen. Hence, the drugs that relieve bronchospasm (bronchodilators) and those that relieve inflammation and hypersecretion (anti-inflammatory drugs) have been developed (Menon 1997).

## **BRONCHODILATORS (QUICK RELIEF DRUGS-RELIEVERS)**

These drugs give rapid relief of symptoms by relaxing the tone of airway smooth muscles, thus making the airways wider and breathing easier. These include:

- Short-acting beta-2-agonist : Salbutamol, Terbutaline, Fenoterol, Albuterol, Isotharine
- Long-acting beta-2-agonist : Salmeterol, Formeterol
- Theophylline
- Anticholinergic drugs : Ipratopium bromide(Ipravent)
- Adrenaline

## **ANTI-INFLAMMATORY DRUGS (LONG-TERM PREVENTORS)**

The drugs which on long-term use, help to prevent the occurrence of asthmatic attacks, are called preventors or controllers. They suppress the inflammatory reactions in asthmatic airways and work slowly to reduce the redness, swelling and sensitivity of the airways and help dry up the mucus. These include:

Solution Corticosteroids: Inhaled (Beclomethasone, Budesonide, Flunisolone and

Triamcinolone), Oral (Prednisolone, Prednisone)

Cromones: Disodium cromoglycate, Nedocromil sodium

A few to more increasing side effects of these drugs have been noticed on prolonged use. For e.g. short acting beta-2-agonists have been found to cause the predictable side effects of palpitations and tremor, especially in patients who use them in high doses intermittently. Theophylline frequently causes nausea, vomiting, headache and restlessness. At high concentration, it causes cardiac arrhythmias and occasionally convulsions. The side effects of high–dose oral corticosteroids taken for prolonged periods have been known for many years. In particular, the effects on the bones and muscles in adults may be more serious than the underlying asthma. With inhaled corticosteroids, hoarseness of voice, candidiasis of the throat and throat irritation may occur (Woolcock 1994).

Thus, although the bronchodilators and anti-inflammatory drugs are effective in controlling asthmatic inflammation, their side effects, as mentioned above, are being increasingly recognized. Therefore, there is a need for developing alternative antiasthma therapies that lack these adverse effects and in particular are specific for asthmatic inflammation. Thus, the belief in non-medicinal, nutritional and natural cure has prompted this trial of Spirulina in asthma patients.

## SPIRULINA: THE SUPREME FOOD-DRUG

Spirulina, the blue green algae, has today emerged as a great nutraceutical phenomenon. Worldwide medical research has discovered that Spirulina with its unique blend of nutrients (good quality proteins, balanced fatty acid profile, antioxidant vitamins and minerals) has helped to combat many health problems like diabetes, arthritis, anemia, cancer etc. Reports have shown that Spirulina *platensis* may be beneficial in treating some forms of atopic bronchial asthma (Hayashi et al 1994). Spirulina could be an ideal choice in such a context for two reasons, firstly it is a rich source of gamma linolenic acid (GLA), which might play a crucial role as an anti – inflammatory agent, and secondly it has a good antioxidant profile that might help to counteract the detrimental exposure to oxidants.

Among the key inflammatory mediators are the n-6 eicosanoids, prostaglandin  $E_2$  (PGE<sub>2</sub>) and leukotriene B<sub>4</sub> (LTB<sub>4</sub>), which are derived from the n-6 polyunsaturated acid (PUFA), arachidonic acid (AA). PGE<sub>2</sub> can cause pain and vasodilation and LTB<sub>4</sub> is a chemo attractant and activator of neutrophils, together they cause vascular leakage and extravasation of fluid (Henderson et al 1987). Many anti-inflammatory pharmacotherapies are directed at inhibiting the production of these inflammatory mediators and thus possibilities exist for therapies that incorporate n-3 and n-6 dietary fatty acid. In such a context GLA, an n-6 fatty acid, possibly plays a crucial role as an anti-inflammatory agent.

Gamma linolenic acid (GLA), generated in the body through the desaturation of linolenic acid by action of the enzyme linoleoyl-CoA desaturase has been shown to be stimulated by insulin and inhibited by epinephrine, cortisol, thyroxine, glucagon and saturated fat (Dayong Wu et al 1999). Lower GLA concentration has also been reported in patients with inflammatory disease (Manker et al 1984, Morse et al 1989, Lindskov et al 1992). Also ingestion of diets rich in GLA elevates dihomo-gamma linolenic acid (DGLA) concentration, resulting in an increase in 1-series of prostaglandins, e.g. PGE<sub>1</sub>, which has potent vasodilatory and anti-inflammatory properties. Thus increase intake of GLA may suppress inflammation through the metabolism of GLA to DGLA and thus competitive inhibition of the 2-series PGs and 4-series LTs (Belch and Hill 2000).

Symptoms of ongoing asthma in adults appear to be increased by exposure to detrimental oxidants, which can be released endogenously in the lungs or can be exogenous in nature. It has also been hypothesized that a deficient antioxidant capacity may also play a role in pathogenesis of asthma (Hatch 1995).

Recent studies have also suggested that an association may exist between a low intake of certain micronutrients and asthma (Montelone and Sherman 1997). Low intake of vitamin C has been associated with wheezing, (Schwartz and Weiss 1990, Bodner et al 1999) increased risk of bronchial hyper responsiveness (Soutar et al 1997) and reduced level of FEV1 (Britton et al 1995, Schwartz and Weiss 1994). Dietary intake of vitamin E has a positive influence on wheezing and lung function (Dow et al 1996). Low intake of vitamin A has been shown to be associated with airflow limitation (Morabia et al 1989). Spirulina can thus be an effective therapeutic mode for combating detrimental damage and inflammation in the respiratory lining as it contains all the antioxidant nutrients in ideal amounts.

Thus with an aim to assess the effectiveness of spirulina supplementation in relieving bronchial obstruction in asthma patients, the study was carried out with following objectives:

- 1. To study clinico-biochemical profile and pulmonary function status of asthma patients.
- 2. To study the effect of spirulina supplementation on the protein status and IgE status of the asthma patients.
- 3. To study the effect of spirulina supplementation on the pulmonary function status of the asthma patients.

## At a glance.....

Bronchial asthma is a common respiratory disorder with increasing, prevalence, mortality and cost of care

- Ut is a chronic inflammatory disease involving many interacting cells which release a whole variety of inflammatory mediators that activate several target cells in the airway, resulting in bronchoconstriction, microvascular leakage and oedema, mucus hypersecretion and stimulation of neural reflexes It is characterised by episodic intra-thoracic airway obstruction, airway hyper responsiveness and airway inflammation.
- Characteristically patients with asthma have some combination of dyspnoea, wheeze, chest tightness and cough. The symptoms of asthma may vary from person to person and from time to time.
- The common asthma triggers (factors that make asthma worse) include viral infection, allergens such as domestic dust mites, animals with fur, cockroach, pollens and molds, tobacco smoke, air pollution, strong emotional expression, chemical irritants and drugs (aspirin and beta blockers).
- The goals in asthma management include
  - Relieve symptoms and stop attacks Prevent long-term risks
  - Restore normal airway function
  - $\diamond$  Require little or no quick relief medication  $\diamond$  Avoid side effects of drugs

Medications used to control asthma include two types. long-term preventive medication (especially anti-inflammatory agents) that keep symptoms away and attacks from starting and quick-relief medication (short-acting bronchodilators) that work fast to treat attacks or relieve symptoms

- Since the side effects of these drugs on prolonged use are being increasingly recognized, the belief in non-medicinal, nutritional and natural cure has prompted this trial of Spirulina in asthma patients.
- Spirulina could be an ideal choice in such a context for two reasons, firstly it is a rich source of gamma linolenic acid (GLA), which might play a crucial role as an anti inflammatory agent, and secondly it has a good antioxidant profile that might help to counteract the detrimental exposure to oxidants.
- Showing objectives
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  - 3. To study the effect of spirulina supplementation on the pulmonary function status of the asthma patients.





Unlike many diseases, which can be attributed to the life-style of modern man, asthma is an ancient illness. The term asthma actually comes from the Greek word '*panos*', which means to pant or to breathe with an open mouth. The Greeks had a great deal of respect for panos, or asthma, as they believed it was sacred disease that signified a visit from the Gods.

## **ASTHMA HISTORIANS**

In the first century A.D., Aretaeus, a Greek physician, noted that women were more prone to asthma, men were more likely to die of it, and children had a better outlook for recovery from it. In the second century, A.D., Galen, the consulting physician to many Roman emperors described asthma as a seizure-like disorder of the lungs. He correctly recorded that asthma was probably due to an obstruction of the bronchial tubes.

One of the more spectacular success stories in asthma folklore involved Archbishop Hamilton of Saint Andrews, who was a lifetime asthma sufferer. In 1552, the wheezing archbishop sent for a famous physician of that era, Girolama Cardano, who then attended the archbishop for more than three months. Cardano set up a rigorous routine of full exercise and proper diet and he also removed a leather pillow and large feather bed from the archbishop's bedroom. After that the archbishop improved dramatically and Cardano's success was widely publicized. The removal of leather pillow and feather bed was probably the reason for the archbishop recovery, making this the first widely quoted case that pointed out the value of using environmental controls in the treatment of asthma. Van Helmont, a famous physician who also suffered from asthma became the first doctor to associate smoke and irritants with asthma. Thomas Siddenheim, who was called the English Hippocrates, appropriately labeled asthma as a lung condition in which the bronchial tubes were all "stuffed up". The first really important American contribution appeared in 1830, when Eberle stressed the important role of heredity and infection in asthma.

In 1835 asthma research took a giant leap forward when Laennec invented the Stethoscope. Doctors could now hear and actually pinpoint the classic physical signs of asthma, wheezing. In 1850 Gerhardt wrote that asthma could be triggered by chemical odours, strong perfumes and changes in temperature or humidity. In 1864 Dr.H.Salter discovered that animal dander could trigger asthma, and by 1900 it was generally accepted that asthma and hay fever are closely related disorders. Early 20<sup>th</sup> century studies that focused on the premise that asthma was a pure psychosomatic illness briefly sidetracked the major advances looming on the horizon. Eventually researchers refuted these erroneous psychiatric theories and proved that asthma was a true physical illness with multiple causes (Hannaway 1996).

## THE RESPIRATORY TRACT: STRUCTURE

A thorough knowledge and appreciation of the structure of the respiratory tract is central to the understanding of asthma. Structurally, the respiratory system may be divided into two: the upper respiratory tract and the lower respiratory tract.

The upper respiratory tract comprises the nose, the pharynx and the larynx and serves many important functions such as heat exchange (to warm inspired air), humidification (to moisten inspired air), filtration (to trap dust and particulate matter in inspired air), sense of smell (olfactory organs) and speech (larynx).

The lower respiratory tract comprises the trachea, the bronchi and bronchioles and divides at its lower end into right and left main bronchi. It owes its rigidity to the C- or Y- shaped cartilaginous rings in its walls, although its posterior wall is composed only of smooth muscle.

**BRONCHI:** The right and left main stem bronchi are passageways between the trachea and lungs. The larger bronchial branches have cartilage rings, which diminish and fade away as smaller branches are formed.

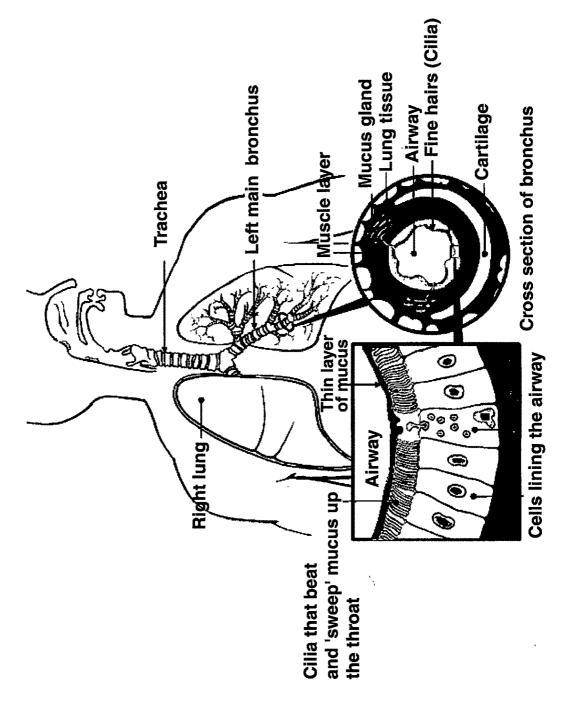
**BRONCHIOLES:** These are smallest subdivision of bronchi, having no cartilage rings and have walls composed, in part, of elastic tissue running longitudinally and an overlying layer of smooth muscle bundles. In the course of over 20 repeated divisions, the bronchial tree descends from primary to secondary bronchi to bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts and sacs and finally to alveoli.

ALVEOLAR DUCTS AND ALVEOLI: The respiratory bronchioles give way to alveolar ducts and increasing number of alveoli. The alveoli are arranged as clusters of thin walled outpocketing from the alveolar ducts. In addition, small outpocketing from the thin walled respiratory bronchioles also occur, these structures are also alveoli which are identical to those arising from the alveolar ducts. In man approximately  $300 \times 10^6$  alveoli comprise between 55 to 60% of total lung volume. Each outpocketing or alveolus is sometimes called an air cell and cluster of air cells is known as the alveolar sac. Figure 3 depicts the structure of lung showing the bronchus. The trachea, bronchi and bronchioles are tubular structures consisting of:

- Innermost mucus lining having mainly ciliated epithelial cells and several mucus secreting goblet cells. The mucus secretion gets enhanced by histamines, bradykinins, serotonin, prostaglandins and stimulation of the parasympathetic nerve fibres in the lungs.
- Submucus layer having blood capillaries, nerve fibres (both sympathetic and parasympathetic) and mast cells containing chemical mediators like histamine etc in their cytoplasmic granules.
- Muscular layer with circular fibres. These muscles get contracted by histamines etc. leading to bronchospasm in bronchioles, and
- Outermost the fibrous layer consisting of elastic fibres (Pearson 1990, Weiss 1975).

## FIGURE 3

## STRUCTURE OF LUNG SHOWING THE BRONCHUS



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## **PATHOGENESIS**

Asthma used to be considered a bronchospastic disease with the treatment directed at airway smooth muscle. However, histopathologic study of airway from patients with asthma who died during severe attack of asthma has shown that an inflammatory response plays a dominant role rather than the airway smooth muscle response. These patients exhibit airway inflammation even when they are symptom free.

Many different cells are involved in the pathogenesis of asthma and they produce a variety of inflammatory mediators which are released into the airway where they interact in a complex manner that activate several target cells in the airway resulting in bronchoconstriction, microvascular leakage leading to submucosal oedema, mucus hypersecretion, plugging of airway lumen by viscid mucus and stimulation of neural reflexes. There is cellular infiltration particularly by eosinophils and epithelial damage.

The human airways are controlled by myogenic, neurogenic and chemical mechanism. The activity originates in the smooth muscles and the blood-borne and locally -derived substance bring about chemical control. The attempt to elucidate the mechanism of bronchial asthma have shown that bronchial hyperresponsiveness is the essential pathophysiologic abnormality. The responses are two fold as:

- (1) Bronchoconstriction and
- (2) Airway inflammation.

## BRONCHOCONSTRICTION

Bronchoconstriction may be provoked by specific agents (triggers) that act through an immunologic mechanism. Inhalation of an allergic substance into the lower respiratory tract may produce in a small group of population IgE antibodies. Any subsequent exposure to such substance produces a series of immunologic and biochemical reaction leading to asthma. Binding of allergens to cell-bound IgE occurs on mast cell or basophils. There is cross-linking of two cell bound IgE molecules by the allergen molecule, influx of calcium ions and subsequent mast cell or basophil degranulation and release of mediators resulting in immediate hypersensitivity response. Protein substances such as pollens, grains, weeds, moulds, house dust, mite, animal dander and non-protein substance such as platinum salts, toluene diisocyanate and trimellitic anhydride elicit immunologic response via IgE dependent interaction.

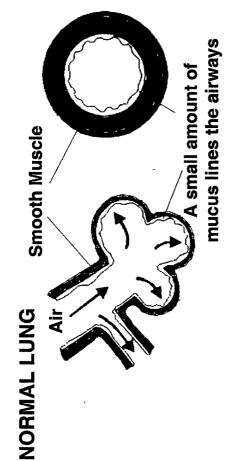
## **AIRWAY INFLAMMATION**

The inflammation causes the airways to be overly sensitive or "twitchy". This twitchiness causes the narrowing and blockage of the airways. As the inflammation increases, the airways become more sensitive and over reactive. During an asthma episode, the mucus-producing cells within the airways increase their output and the mucus plugs the airway. The combination of airway narrowing, mucus plugging, and airway inflammation can block portions of the airway entirely (Figure 4).

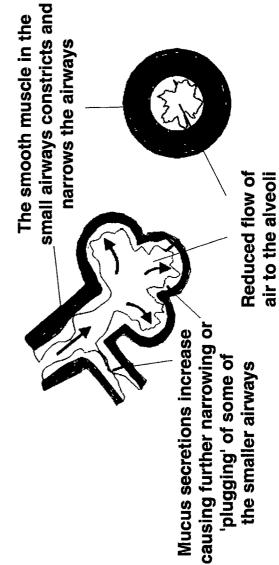
Marked inflammation in the airways is observed with infiltration of inflammatory cells especially eosinophils, epithelial cells, sloughing into lumen and plugging of the airway lumen with viscous mucus. There is smooth muscle hyperplasia. Biopsy study

## **FIGURE 4**

# STRUCTURE OF LUNG DURING AN ASTHMA ATTACK



## LUNG DURING AN ASTHMA ATTACK



of airway in mild asthmatics has revealed airways shedding of ciliary epithelium, collagen deposition beneath basement membrane, partial mast cell degeneration and eosinophilic cell infiltration of lamina propria (Shankar 1996).

## **INFLAMMATORY CELLS**

Asthma, a chronic inflammatory disease involves multiple interacting cells. The inflammatory stimuli to the airways activate cells normally found in the lungs referred to as primary effector cells. These include mast cells, basophils, alveolar macrophages, epithelial and endothelial cells of the airways. On activation they release mediators that are chemotactic for cells derived from the circulation. They are referred to as secondary effector cells and include eosinophils, neutrophils, T-lymphocyte and platelets. These cells and their mediators (preformed or generated) modulate airway activity (Figure 5).

## Mast cell

The mast cell has long been considered to be of paramount importance in the pathophysiology of asthma. They are present in the lining of bronchioles and bronchi beneath the basement membrane and adjacent to the capillaries. The key role of mast cells is during the IgE-mediated allergic reaction and thus the early asthmatic response is well documented .In addition, there is evidence that it responds to non-IgE stimuli in the airway-for e.g., changes in the osmotic cellular environment associated with such challenges as exercise, hyperreactivity and hypotonicity (Black 2002). The array of mediators released from the activated mast cell is diverse including prostaglandins, leukotrienes, cytokines, such as interleukin 1,2,4,10 and 13;growth