CHAPTER -1

INTRODUCTION

1.0 Definition of COPD

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow obstruction with breathing–related symptoms such as chronic cough, exertional dyspnea, expectoration, and wheeze (Rennard, 1998). These symptoms may occur in conjunction with hyper responsiveness and may be partially reversible.

COPD is also known as Chronic Obstructive Lung Disease (COLD), Chronic Obstructive Airways Disease (COAD), Chronic Airflow Limitation (CAL), and Chronic Obstructive Respiratory Disease (CORD), is the co-occurrence of chronic bronchitis and emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed [(U.S. National Heart Lung and Blood Institute; Signs and Symptoms MedlinePlus Encyclopedia Chronic Obstructive Pulmonary Disease) (http://www.nhlbi.nih.gov/health/dci/Diseases/Copd/Copd Signs And symptoms html)].

This leads to limitation of the flow of air to and from the lungs, causing shortness of breath. In clinical practice, COPD is defined by its characteristically low airflow on lung function tests (Nathell *et al.*.,2007).COPD includes chronic obstructive bronchiolitis with fibrosis and obstruction of small airways, and emphysema with enlargement of air spaces and destruction of lung parenchyma, loss of lung elasticity and closure of small airways. Chronic bronchitis, by contrast, is defined by a productive cough of more than 3 months duration for more than two successive years; this reflects mucus hypersecretion and is not necessarily associated with airflow limitation. Most patients with COPD have all three pathological mechanisms (chronic obstructive bronchiolitis, emphysema and mucus plugging) as all are induced by smoking, but may differ in proportion of emphysema and obstructive bronchiolitis (Barnes, 2000).

1.1.1 Chronic Bronchitis

Chronic Bronchitis is defined as chronic or recurrent (coughing of sputum on most days during at least three consecutive months in two successive years) bronchial mucus hypersecretion resulting in chronic expectoration when other causes such as bronchiectasis or tuberculosis have been excluded (Ciba Guest Symposium Report, 1959; Sifakas *et al.*, 1995).

Chronic Bronchitis is further sub-divided into

(i) simple chronic bronchitis with chronic or recurrent mucoid hypersecretions
(ii) chronic or recurrent mucopurulent bronchitis when the sputum is persistently or intermittently mucopurulent; and
(iii) chronic obstructive bronchitis, when there is airflow limitation as measured by physiological measurements.

1.1.2 Emphysema

Emphysema is defined pathologically as "a condition of the lung characterized by abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of their walls, and without obvious fibrosis". Destruction in emphysema is defined as non uniformity in the pattern of respiratory airspace enlargement so that the orderly appearance of the acinus and its components is disturbed and may be lost (Snider *et al.*, 1985).

1.2 Global Initiative for Obstructive Lung Disease (GOLD) CRITERIA FOR COPD

Several different definitions have existed for COPD (American Thoracic Society, 1995; Siafakas *et al.*,1995).A widely accepted definition from GOLD defines COPD as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases" (Pauwels *et al.*, 2001).

The definition of COPD adopted by the Global Initiative on Obstructive Lung Disease (GOLD) for the first time encompasses the idea that COPD is a chronic inflammatory disease and much of the recent research has focused on the nature of this.inflammatory.response.[(GOLD,2003).www.goldcopd.com/workshop/index.html.)].

1.3 RISK FACTORS OF COPD

Several risk factors have been reported in different epidemiological studies. Tobacco smoking (Jindal *et al.*, 2006b) is the most important identifiable factor in almost all the reports. Male sex, advancing age, lower socioeconomic grouping and urban residence are also associated with increased occurrence of COPD. Exposure to Environmental Tobacco Smoke (ETS), and exhausts of fuel combustion are also important especially among non-smoker patients and women (Chhabra *et al.*, 2001; Jindal *et al.*, 2006b). COPD is the consequence of an abnormal inflammatory response to inhalation of noxious agents such as cigarette smoking, occupational exposure and environmental factors. However, individual factors also play an important role (e.g., enzymatic deficiencies, immunological trouble)and in fact only a portion (10-20%) of heavy smokers develop a clinically detectable disease (Hogg,2004; Piqueras *et al.*, 2001). The other factors include, aging, occupational exposure, and air pollution.

1.3.1 Natural History of COPD

The FEV_1 in asymptomatic healthy nonsmokers declines by 25 to 30 ml per year at about the age of 35 years. The rate of decline is steeper for smokers and the rate of fall is directly proportional to the severity of smoking (Snider *et al.*, 1994). The decline in function occurs in a slowly accelerating curvilinear path. In most subjects, the loss is uniform, and in some it develops in stages. There is a direct relationship between FEV_1 level and the slope of FEV_1 decline (Burrows *et al.*, 1987a).The relationship is also direct with the initial FEV_1 / FVC particularly in men (Burrows *et al.*, 1990). The fall in PEFR in both the symptomatic and asymptomatic males showed a decline of about 5L/ min/ year. The fall was negligible in women over a period of 10 years, both symptomatic and asymptomatic (Burrows ,1987b).Other risk factors are age , lifetime smoking history , and the number of cigarettes currently smoked (Peto *et al.*,1983).Acute chest illness, which is common in COPD , decreases lung function for about 3 months (Burrows *et al.*,1987a).The role of mucus hypersecretion on the mortality is unclear (Buist *et al.*,1984). It was earlier believed that small airways (those less than 2mm in diameter) obstruction as calculated from closing volumes ,closing capacity , and the slope of the alveolar plateau derived from a single breath nitrogen test may be good predictors of development of COPD subsequently . However, it is proved now that this is not so (Anthonisen *et al.*,1994). Ventilatory function tests indicating emphysema (DLCO, FRC, TLC) predict survival in a minor

way (Camilli *et al.*,1987). After smoking cessation , a small amount of lung function is regained. About 35 % of subjects in the Lung Health Study who stopped smoking , for one year showed an increase in postbronchodilator FEV_1 of about 57 ml in opposed to 38 ml who did continued smoking (Higgins *et al.*,1982).Thereafter ,the rate of lung function declines slows to approx. that seen in never smokers of the same age (Postma *et al.*,1989).Other reports suggest that subjects who have a more rapid decline in lung function can be declined by greater loss of FEV_1 or FEV_1 / FVC ratio (Flenly,1986).Smoking cessation improves prognosis regardless of age (Janhoff *et al.*,1987).

1.4 SIGNS AND SYMPTOMS

1.4.1 Chronic Obstructive Pulmonary Diseases

Three disorders are incorporated in COPD :emphysema, peripheral Airway Disease, and Chronic Bronchitis(ATS,1987;Murray,1997).Any individual patient may have one or all of these conditions, but the dominant clinical feature in COPD is always impairment, or limitation of expiratory common causes. These figures are expected to increase upto 4.1 % and move to 5^{th} rank by 2020 (Jindal, 2006a).

One of the most common symptoms of COPD is shortness of breath dyspnea (Mahler,2006). People with COPD typically first notice dyspnea during vigorous exercise when the demands on the lungs are greatest. Over the years, dyspnea tends to get gradually worse so that it can occur during milder, everyday activities such as housework. In the advanced stages of COPD, dyspnea can become so bad that it occurs during rest and is constantly present.

Other symptoms of COPD are a persistent cough, sputum or mucus production, wheezing, chest tightness, and tiredness [(U.S. National Heart Lung and Blood Institute; Signs and Symptoms MedlinePlus Encyclopedia.(http://www.nlm.nihgov/medlineplus/ency/article/00091.htm).]

People with advanced (very severe) COPD sometimes develop respiratory failure. When this happens, cyanosis, a bluish discoloration of the lips caused by a lack of oxygen in the blood, can occur. An excess of carbon dioxide in the blood can cause headaches, drowsiness or twitching

(asterixis). A complication of advanced COPD is cor pulmonale, a strain on the heart due to the extra work required by the heart to pump blood through the affected lungs [(MedlinePlus Encyclopedia *Chronic Obstructive Pulmonary Disease)* (http://www.nlm.nihgov/medlineplus/ency/article/00091.htm).]

Symptoms of cor pulmonale are peripheral edema, seen as swelling of the ankles, and dyspnea.

There are a few signs of COPD that a healthcare worker may detect although they can be seen in other diseases. Some people have COPD and have none of these signs. Common signs are:

- tachypnea, a rapid breathing rate
- wheezing sounds or crackles in the lungs heard through a stethoscope
- breathing out taking a longer time than breathing in
- enlargement of the chest, particularly the front-to-back distance (hyperaeration)
- active use of muscles in the neck to help with breathing
- breathing through pursed lips
- increased anteroposterior to lateral ratio of the chest (i.e. barrel chest).

1.5 DIAGNOSIS

Essentials of diagnosis include:

- History of cigarette smoking.
- Chronic cough and sputum production (in chronic bronchitis)
- Dyspnea
- Rhonchi, decreased intensity of breath sounds, and prolonged expiration on physical examination
- Airflow limitation on pulmonary function testing that is not fully reversible and most often progressive

The diagnosis of COPD should be considered in anyone who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease such as regular

tobacco smoking (Rabe etal,2007).No single symptom or sign can adequately confirm or exclude the diagnosis of COPD,(Holleman *et al.*,1995) although COPD is uncommon under the age of 40 years.

1.5.1 Spirometry

The diagnosis of COPD is confirmed by spirometry,(Rabe *et al.*,2007) a test that measures the forced expiratory volume in one second (FEV_1), which is the greatest volume of air that can be breathed out in the first second of a large breath. Spirometry also measures the forced vital capacity (FVC), which is the greatest volume of air that can be breathed out in a whole large breath. Normally, at least 70% of the FVC comes out in the first second (i.e. the FEV_1/FVC ratio is >70%). A ratio less than normal defines the patient as having COPD. More specifically, the diagnosis of COPD is made when the FEV_1/FVC ratio is <70%. The GOLD criteria also require that values are after bronchodilator medication has been given to make the diagnosis, and the National Institute for Clinical Excellence (NICE) criteria also require FEV1% (Nathell *et al.*,2007). According to the ERS criteria, it is FEV1% predicted that defines when a patient has COPD, that is, when FEV1% predicted is < 88% for men, or < 89% for women (Nathell *et al.*,2007).

Spirometry can help to determine the severity of COPD (Rabe *et al.*, 2007).The FEV_1 (measured after bronchodilator medication) is expressed as a percentage of a predicted "normal" value based on a person's age, gender, height and weight:

Severity of COPD	**FEV_1 % predicted**
Mild	≥80
Moderate	50–79
Severe	30–49
Very severe	<30 or chronic respiratory failure symptoms

Table 1: Assessment of severity of COPD (Celli *et al.*, 2004)

The severity of COPD also depends on the severity of dyspnea and exercise limitation. These and other factors can be combined with spirometry results to obtain a COPD severity score that takes multiple dimensions of the disease into account (Celli *et al.*, 2004).

1.5.2 Other tests

On chest x-ray, the classic signs of COPD are overexpanded lung (hyperinflation), a flattened diaphragm, increased retrosternal airspace, and bullae (Torres *et al.*, 2007). It can be useful to help exclude other lung diseases, such as pneumonia, pulmonary edema or a pneumothorax (Torres *et al.*, 2007).Complete pulmonary function tests with measurements of lung volumes and gas transfer may also show hyperinflation and can discriminate between COPD with emphysema and COPD without emphysema.

1.6 THE COPD BURDEN

The data from most of the Asian countries are patchy, but it clearly points towards a huge burden (Jindal,2006a).Using a mathematical model to estimate the prevalence of COPD, the combined prevalence in 12 Asia –Pacific Countries and regions was 6.3% which was higher than the overall rate of 3.8% as extrapolated from WHO data for this region(Regional COPD Working Group, 2003).The total burden was estimated at 56.6 million patients of moderate to severe COPD. However, there were no estimates on COPD prevalence for India and other countries of the Indian sub-continent in this report. But, the field data of India is said to reflect similar trends (Jindal *et al.* ,2006a). COPD is one of the leading causes of mortality. By 2020 it is expected to rise to the third position as a cause of death and at fifth position as the cause of disability adjusted life years (DALYs) as per projections made in Global Burden of Disease study (GBDS) (Jindal *et al.*, 2006a).

COPD is a leading cause of morbidity and mortality worldwide, affecting over 44 million people (Murray CJ *et al.*, 1996). Cigarette smoking is the most important risk factor for developing COPD globally (Tager *et al.*,1976; Xu X *et al.*, 1992). There are reports where COPD is associated with a doubling or tripling of the rate of decline in the forced expiratory volume in

one second (FEV_1) (Chan-Yeung *et al.*,2007)and a 2-20 fold increase in the risk of death from COPD(Doll *et al.*,1964a;Doll *et al.*,1964b).

COPD in India has been recognized and investigated with the help of small surveys conducted in different populations in the last 40 years. Prevalence rates varying from about 2 to 22% in men and from 1.2 to 2 percent in women have been shown indifferent reports (Reddy *et al.*, 2004).

The relative prevalence and severity of mining related occupational lung diseases are a function of the commodities mined, airborne hazard exposure levels, and co-existing illnesses or environmental conditions and lifestyle. The contamination of atmosphere from anthropogenic sources such as coal mining, industrial sources as well as local conditions generated either in home or workplace make a significant contribution as environmental factors, to development of COPD. The coal-based industries in India are considered to be one of the chief industrial emitters in India. North East part of India has coals with different physicochemical properties compared to other Indian coals (Khare *et al.*, 2011). They have high sulphur and volatile matter with low ash and moisture contents. The human health effects of poor air quality are far reaching, but principally affect the body's respiratory system and the cardiovascular system.

Besides environmental factors, exposure to other factors such as oxidative injury also plays an important role in the pathogenesis of COPD (Repine *et al.*, 1997). Such injury, resulting from an imbalance between free radicals and protective mechanisms can alter the conformation of protease inhibitors and reparative enzymes, injure cell membranes, and result in mutagenesis. Free radicals appear in the lung by inhalation from the environment or by release from inflammatory cells. Genetically controlled antioxidant defense systems may also play an important role in determining susceptibility, both to free radicals released by inflammatory cells and to oxidants inhaled from the environment. The lungs possess several enzymatic scavengers including glutathione which are under genetic control. The observations that the enzymatic antioxidants are under genetic control and that allelic variation alters their abilities to reduce free radicals (Koyama *et al.*,1998;Smith *et al.*,1997) suggest that genetic factors may place some persons at greater risk for oxidant injury. The glutathione system is the major antioxidant mechanism in the airways. The increased oxidative stress in the airways of COPD patients may play an important pathophysiological role in the disease by amplifying the inflammatory response in COPD. Several common variants of GSTs have been well characterized and are

associated with certain respiratory diseases (Hayes *et al.*, 2000). The GSTM1 and GSTT1 genes are located on chromosomes 1p13 and 22q11.2, respectively and are actively engaged in the detoxification of cigarette smoke and environmental xenobiotics (Mehrotra *et al.*,2010)**.**These genes are expressed in the respiratory tract and have common functional variant alleles that result in either a total absence or a substantial change in enzyme activity.

Susceptibility to COPD is not a single gene event and ethnic differences exist (Mehrotra *et al.*,2010).The present study was undertaken at opencast coal mine area at Ledo, near Tirap in Assam (Lat. 27º13'-27º23'N and Long. 95º35'-96'00E). This coal field was initiated in the year 1870 (Akala, 1995) and is now operated in the name of North –Eastern Coalfields, Coal India Limited (NECF-CIL), Margherita. There is about 1.00 billion tonnes coal reserves estimated in this coal bearing zone of North-East India which is 0.5% of the country's total reserve of about 200 billion tones (Chaoji,2002). Assam alone produces 375.4 million tonnes of coal per annum.

Among the most prevalent occupational lung diseases in the world are those induced by inhalation of mineral dusts such as asbestos, silica and coal dust (Mossman *et al.*,1990). Excavation of Coal by Open Cast Mining through mechanized process is in progress at two places at Tiklok and the other one is at mining Ledo- Tirap (Lat. 27º13'-27º23'N and Long. 95º35'-96'00E) in Upper Assam areas. High ash content in Indian Coals and inefficient combustion technologies contribute emissions to air, particulate matter and other trace gases.

Although everyone is at risk from the health effects of air pollution, certain sub-populations are more susceptible. Children and newborns are also sensitive to the health effects of air pollution since they take in more air than adults for their body weight and consequently, a higher level of pollutants. The present study was carried out with special concern on the incidence of respiratory symptoms due to continuous coal dust exposure in the population staying very near to the open-cast coal mine of Ledo, Assam. Opencast coal mining is more severe an air pollution problem in comparison to underground coal mining. Opencast mining create much more air quality deterioration in respect of dust and gaseous pollutants. It creates air pollution problem not only within the mining premises but also in surrounding residential area affecting abundant air quality (Singh, 2008).

Chronic respiratory diseases have a pre-eminent role in the health conditions of coalminers with implications for morbidity and excess mortality from specific causes. (Morgan *et al.*, 1980).

Oxidative stress may also impair the function of antiproteases such as α_1 – antitrypsin (α_1 AT) and SLPI,and thereby accelerates the breakdown of elastin in lung parenchyma (Taggart *et al.*,2000).Normally proteases are counteracted by an excess of endogenous antiproteases .The major inhibitors of serine proteases are α_1 AT in the lung parenchyma and airway epithelium derived SLPI in the airways (Rooney *et al.*,2001).The best described deficiency that results in early onset emphysema is the ZZ type on which a single amino acid substitution (Gly342-Lys) results in structural alterations in α_1 AT resulting in the failure of its normal posttranslational modification and secretion by hepatocytes leading to very low plasma concentrations (Carp *et al.*,1978).

Studies using radical scavengers or antioxidants have underscored the significance of ROS in dust-elicited lung toxicity including pulmonary fibrosis and genotoxicity (Dong *et al..*, 1994; Driscoll *et al..*,1997).Based on these observations, adverse oxidative effects have been suggested to be related to to an impaired balance between ROS and antioxidant defense status ,and upregulation of antioxidant enzymes is considered as a marker of oxidative stress(Janssen *et al..*,1994).

There are reports where COPD is associated with a doubling or tripling of the rate of decline in the forced expiratory volume in one second (FEV_1) (Chan-Yeung *et al.*,2007) .While active cigarette smoking is clearly important, only 25% of continuous smokers were found to develop COPD (Lokke *et al.*,2006) suggesting that individual susceptibility or genetic factors may play a role.Alpha-1-antitrypsin deficiency is a well recognized factor for COPD (Laurell *et al.*,1963).

Occupational lung diseases comprise a group of disorders caused by inhalation of a wide variety of harmful materials, dust, microorganisms, smoke, allergens, vapours, fumes, etc. Although these substances are present in the general environment, most of them occur in work related environments in greater concentrations resulting in a variety of lung reactions including the lung parenchyma and the airways (Bechlek, 1991).

It is an established fact that chronic respiratory diseases have a pre-eminent role in the health conditions of coalminers with implications for morbidity and excess mortality from specific causes (Morgan, 1980).This study is an attempt to report the coal dust "exposure-response" relationship amongst the people residing very near to the open-cast coal mine areas in Ledo, Assam where coalmining is more than a century old practice; and also to trace out the genetic susceptibility with respect to GSTM1 , GSTT1 and A1AT to the disease in the population.

The following hypothesis and objectives were designed:

1.7 HYPOTHESIS

1) The people involved in coal mine operation and residing near the open cast coal mine may suffer from respiratory diseases resulting in severe disease condition such as Chronic Obstructive Pulmonary Disease (COPD).

2) Some of the populations may be genetically predisposed to the disease due to genetic alteration in GSTT1, GSTM1 or α_1 – antitrypsin (α_1 AT) genes; with referance to COPD.

1.8 OBJECTIVES

Based on the above hypothesis, the following objectives have been designed**:**

1) Air analysis of the site under study will be done which includes 0-15kms around the vicinity of open cast coal mines at Ledo, Assam.

2) Lung function analysis of the people living in the vicinity of the above site.

3) To study the genetic alteration / makeup in GSTT1, GSTM1, α_1 – Antitrypsin gene in Chronic Obstructive Pulmonary Disease (COPD) compared to control population.

4) To analyse the statistical correlation of genetic alterations of the above genes ,lung function analysis with disease severity.