GENERAL INTRODUCTION
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Tobacco smoking has been established as one of the most important causes of chronic bronchitis. When allowed to progress, this disease results in severe disability and finally respiratory failure. While the relationship between prolonged smoking and the development of chronic bronchitis is well authenticated, there is little knowledge concerning the changes in pulmonary function that precede the appearance of the overt manifestations. The usual pulmonary function tests show no apparent change in lung function in the early stages and yet the detection of possible abnormalities in this phase is crucial, because the symptoms once fully developed, are irreversible and refractory to treatment. Moreover, there is evidence to suggest that in the early stage the pathological changes may be reversed by the cessation of smoking. Therefore, detection of the early effects of smoking on lung function is of great practical importance, in terms of prevention and therapy.

There are three basic aspects to the problem of assessing the incipient stages of any functional derangement. Firstly, the recognition of these changes in function as early as possible, by developing a simple, sensitive and easily reproducible test which can be quantitated sufficiently to yield valid data. The
second aspect of the problem is to assess the consequence of this derangement to the individual. The early stages of any chronic disease are often symptomless at normal levels of activity. Therefore, marginal deficiency in function may only become apparent when the functional reserves of a system or organ are fully stretched. It thus becomes necessary to subject the system or organ to the limits of physiological stress to detect minimal deficits in function. The functional consequence to the individual, of early abnormalities in the system may thus be detected. The third aspect is the study of the variation in individual response, to the etiologic agent causing the derangement.

This thesis is an account of an integrated study of these three aspects in relation to the early effects of cigarette smoking on pulmonary function. The bearing that these aspects have on the planning of this study is explained more fully in the later sections of this chapter. These considerations may be better appreciated after a preliminary discussion on the characteristics of tobacco smoke, the nature of its action on the respiratory system, and the defence mechanisms of the airways against these actions.

**Characteristics of tobacco smoke**

Tobacco smoke is a heterogeneous mixture of gases, uncondensed vapours and liquid particulate matter. The
smoke enters the mouth as a concentrated aerosol with billions of particles per ml. The average size of these particles is about 0.5 microns and almost all particles are less than 2 microns.

The composition of cigarette smoke is influenced to some extent by the temperature attained at the burning end of the cigarette. When the smoke is inhaled by drawing air through the cigarette, the temperature reached is approximately 884°C. At this temperature many of the constituents of tobacco undergo extensive chemical changes and some five hundred different compounds have been identified in the smoke. For purposes of studying its biological properties, the smoke is separated into a particulate phase and a gas phase. Carcinogenic hydrocarbons and nicotine with its allied compounds are found in the particulate phase. The particulate phase may be removed from the inhaled smoke to a limited extent by the use of various types of filters in the cigarettes. The gas phase is composed of gases such as carbon monoxide, hydrogen cyanide, ammonia, formaldehyde, nitrogen, oxygen and methane.

Mechanism of particle deposition

The three important physical processes which determine particle deposition in the lungs are inertial impaction, sedimentation and diffusion. Inertial impaction and sedimentation are the chief mechanisms
by which the larger particles of sizes ranging from a few microns to more than 100 microns get deposited. Sedimentation is the major mechanism for particles of intermediate size ranging from 0.1 micron to greater than 50 microns. Diffusion or Brownian movement is the predominant mechanism of deposition for particles smaller than these. The site of deposition depends on the physical process involved and on the particle size. Inertial impaction takes place in the upper respiratory tract. Sedimentation occurs chiefly in the smaller bronchi and bronchioles, and diffusion occurs mostly in the alveoli. As almost all the particles in cigarette smoke are less than 2 microns, these get deposited chiefly in the smaller bronchi, bronchioles and alveoli. Available evidence suggests that even if the tobacco smoke is held in the lung for a relatively short period such as 2 to 5 seconds, about 80% to 90% of the particles are retained in the respiratory tract and the alveoli.

**Sites of action**

Thus, the three major sites of action of tobacco smoke are:

1. the bronchi, where it can cause paralysis of the cilia, mucous gland hyperplasia, hypersecretion of mucus and increased susceptibility to infection.
2. the terminal bronchioles, where it can cause inactivation of surfactant, premature closure leading to inequalities of ventilation perfusion ratios (V/Q), inflammatory and exudative changes and goblet cell metaplasia.

3. the alveoli, where it can adversely affect gas exchange due to V/Q inequalities and also cause cellular infiltration and release of proteolytic enzymes. These enzymes may then cause alveolar destruction.33

**Particle clearance**

The clearance of the mammalian respiratory system is dependent upon the efficient integrated functioning of a complex mechanism. Extending from the nose to the terminal bronchioles, is a mucous layer in which impacted particles and dissolved materials reside. The rhythmic beat of the cilia propels this layer over the surface of the respiratory tract to the exterior. Clearance distal to the terminal bronchioles probably occurs by solution followed by absorption into the vascular or lymphatic system. Some of the particles undergo phagocytosis and are transported to the ciliated passages.222 It is relevant here to note that tobacco smoke has been shown to affect the normal clearance mechanism by inhibiting ciliary motility,27,57,161 causing qualitative and quantitative changes in the mucus secretion,71 and impairing phagocytic activity.221,222
Review of relevant literature

Many major studies have shown the relationship between smoking and respiratory disease. The first of these was a study conducted among 41,000 British physicians. This showed a strong association between smoking and death from bronchitis. The findings from the other studies were similar. Retrospective studies of mortality due to chronic bronchitis in Northern Ireland over a period of 3 years, showed that the mortality rates for both men and women were greater among smokers and were directly related to the number of cigarettes smoked. Studies done on the association of cigarette smoking and morbidity due to respiratory disorders, consistently showed a significantly greater incidence of respiratory signs and symptoms among smokers than among nonsmokers. Prevalence of symptoms increased with the amount of cigarettes smoked. All these findings point to the importance of smoking as an etiological factor in chronic bronchitis.

The early pathological changes in chronic bronchitis are known to occur in airways smaller than 2 mm internal diameter. These include the smallest bronchi and bronchioles and are called the peripheral airways or the small airways. Extensive narrowing of these airways may exist without causing any symptoms, or changes in the routine pulmonary function tests such as the
measurement of lung volumes, total airway resistance and timed vital capacity.\textsuperscript{141} Macklem and Mead (1967)\textsuperscript{137} partitioned the resistance of the intrathoracic airways into central and peripheral components and found that peripheral resistance normally accounted for only a small part of the total pulmonary resistance. Thus, widespread narrowing of these airways could be present, without causing any change in the total airway resistance or lung volumes. The peripheral airways have therefore been regarded as the "Silent Zone" of the lung.\textsuperscript{234}

Though no overt signs or symptoms are caused at this early stage, narrowing of the peripheral airways causes impairment of gas exchange. Anthonisen et al. (1968)\textsuperscript{13} using \textsuperscript{133}xenon, found significant abnormalities in $V/Q$ and gas exchange, in very early cases of chronic bronchitis, although the results of routine lung function tests were within normal limits. They attributed these changes to peripheral airway narrowing. Narrowing of these airways could cause changes in the distribution of ventilation to the air spaces beyond. Even in the presence of collateral channels, the air received by these air spaces through the collateral channels would already have exchanged oxygen and carbon dioxide to some extent during its passage through unobstructed air spaces. However, proportionate changes in perfusion do not appear to occur; therefore, the altered distribution of ventilation leads to inequalities of
\( V/Q \) and abnormalities of gas exchange.\(^{95,139}\)

The strong association between smoking and chronic bronchitis and the fact that the early changes in chronic bronchitis occur in the peripheral airways, led to the search for early peripheral airway changes in smokers. Numerous studies have been reported in this regard. McFadden and Linden (1972)\(^{155}\) studied the pulmonary function of heavy smokers and found that although their lung volumes, forced expiratory volumes (FEV), airway resistance (Raw) and static compliance (Cstat) were not abnormal, they consistently showed frequency dependence of dynamic compliance (Cdyn (1)) and abnormally elevated alveolar-arterial oxygen gradients (A-aDO\(_2\)) at rest and during exercise. The existence of abnormal gas exchange and frequency dependence of Cdyn (1) in the absence of abnormalities in the elastic recoil of the lung and in total airway resistance in these subjects, is strongly suggestive of widespread narrowing of the small airways.\(^{234}\) McCarthy et al. (1972)\(^{151}\) in a study of 66 non-smokers and 46 heavy smokers found evidence of small airway disease in 72% of the smokers. Stanescu et al. (1973)\(^{210}\) studied 16 smokers and 16 nonsmokers who were completely asymptomatic and found evidence of small airway narrowing in the smokers. The study of Buist et al. (1973)\(^{41}\) on a large number of smokers and nonsmokers showed marked alterations in pulmonary function suggestive of peripheral airway narrowing in the smokers.
Dosman et al. (1976) studied 49 smokers and 60 nonsmokers and found that 90% of the smokers but only 5% of the nonsmokers had symptoms of cough, sputum production and wheezing. Mayco and Minette (1976) detected abnormalities in pulmonary function indicative of peripheral airway narrowing in 80 smokers whom they studied. However, these studies were all done on heavy smokers with long smoking histories, who in most instances were not asymptomatic.

The existence of these widespread airway changes in heavy smokers suggests the possibility that even young smokers though asymptomatic may have some early peripheral airway narrowing which could be detected by suitably sensitive tests. Studies on such subjects have been relatively few. Peters and Ferris (1967) studied a group of medical students and found evidence of significant small airway narrowing in the smokers, but these were subjects with varying severity of respiratory symptoms and were not entirely asymptomatic. Seely et al. (1971) studied lung function in relation to smoking in high school students and found changes indicative of small airway obstruction. They concluded that one to five years of regular smoking was sufficient to cause impairment of lung function in teenagers. Lim (1973) demonstrated significant small airway narrowing in 1 out of every 5 smokers among high school students. Ingram and O'Cain (1971) studied a small group of asymptomatic smokers.
and obtained evidence of small airway narrowing in them. Streider and Kazemi (1967) reported their observation of arterial hypoxemia in young asymptomatic smokers. The autopsy studies of Niewoehner et al. (1974) demonstrating the existence of structural changes in the peripheral airways of young asymptomatic smokers are also relevant in this context. These studies indicate the presence of early peripheral airway changes even in young smokers. On the other hand, Ferris et al. (1965) observed that young smokers had higher vital capacities and forced expiratory volumes than young nonsmokers, although the deterioration in these parameters was greater in the smokers. Similarly, a recent study of Tockman et al. (1976) showed that young smokers had better pulmonary function than young nonsmokers when assessed by certain function tests, but exhibited a more rapid deterioration with age. These contradictory findings may possibly be explained by the fact that their subjects formed extremely heterogeneous groups, including those exposed to different environmental conditions and drawn from widely varying ages.

There is thus a need for more investigations on homogeneous populations of young smokers within limited age groups, as the rapidity with which airway changes develop and progress may be affected by the age at which smoking starts and by the simultaneous presence of other environmental detrimental factors that may alter the
effect of smoking on the lung. The

Many studies have shown that early peripheral
airway changes in smokers may be reversed by cessation
of smoking. Ingram and O’Cain (1971) reported that
cessation of smoking by young smokers caused the frequency
dependence of Cdyn (1) to return to normal within 8
weeks. Similar reversibility of peripheral airway
narrowing, abnormal ventilation distribution and impaired
gas exchange have been reported by others. 42, 154, 155

Objectives of the study

The first aspect of the problem of investigating
the effects of tobacco smoking on peripheral airways
is the detection of abnormalities as early as possible.
The impairment of gas exchange that can be caused by
small airway narrowing and the reversibility of this
narrowing in the early stages, make early detection of
these changes in young asymptomatic smokers imperative.
In this context two considerations are of importance.
One is the choice of a suitable test to detect these
early changes. Not only must the test be simple and
reproducible but the determination of its sensitivity
must be based on accepted statistical criteria. 208
The other is the choice of a suitable homogeneous
population for the study of these early changes, so that
the influence of extraneous factors can be minimised.

While the relationship between smoking and lung
damage is well documented in cross sectional studies, there have been very few longitudinal studies on young subjects even over a limited number of years. Such few studies as have been done were in patients with chronic bronchitis,\textsuperscript{29,62,210} and in older heavy smokers.\textsuperscript{42,154} Moreover, the populations studied were not homogeneous and consisted of individuals exposed to different environments. Aberrant relationships between smoking and lung damage may be detected when individuals are exposed to other atmospheric pollutants as well.\textsuperscript{37,125} Therefore, a longitudinal study with adequate controls where both the smokers and the nonsmokers are exposed to the same environment is essential, to provide information on the natural history and progression of the disease.

The second major component of the problem of assessing incipient stages of any functional derangement concerns the study of the consequences of these early changes to the individual as a whole. Although at this early stage, the individual continues to be asymptomatic, the impairment of gas exchange and resultant hypoxemia\textsuperscript{213} caused by the peripheral airway narrowing is likely to have some latent effects. Obviously, the effects of impaired gas exchange are most likely to be on the oxygen uptake (oxygen consumption) of the individual. The oxygen uptake of a resting subject is about 250 ml per minute. This increases with increasing levels of
activity, and at very high work loads may reach values as high as three to four litres per minute. Further increases in work load, usually cause less increments in oxygen uptake until the latter shows no further increase. Work under these conditions is chiefly performed anaerobically, the subject acquiring various degrees of oxygen debt. The increasing oxygen uptake is achieved by increasing blood flow to the muscles and increasing oxygen extraction from the blood in the tissues. Many factors can affect the maximal oxygen uptake of an individual, but one of the most important is arterial hypoxemia, which by decreasing the oxygen available for extraction from the blood in the tissues, can limit the oxygen uptake of an individual. With mild degrees of hypoxaemia, there is likely to be no impairment of oxygen uptake at rest or at low levels of activity. However, at very heavy work loads, when the cardiopulmonary systems reach the limits of physiological stress, the oxygen uptake is quite likely to be impaired. Thus, the determination of maximal oxygen uptake would help to detect the consequences to the individual of marginal deficiency in function resulting from early peripheral airway changes.

The third facet of the study is the evaluation of the differences in individual susceptibility to tobacco smoking. Though tobacco smoking is one of the chief
causes of chronic bronchitis, it is nevertheless important to recognise that constitutional and environmental factors may play a significant role in the rapidity with which the disease develops and progresses.\textsuperscript{30,98,130} Identification of those subjects who are at a high risk of developing the disease is of practical importance as efforts at inducing subjects to stop smoking would naturally have to be concentrated more on these individuals. The nature of the immediate response of an individual to smoking may provide some information on his susceptibility to the long term effects of tobacco smoke. There are probably large differences in the immediate response of individuals to smoking. Hence it is possible that those who exhibit a marked immediate response to smoking are those who also have an enhanced susceptibility.\textsuperscript{36} If a relationship exists between the nature or magnitude of the immediate response and the decline in pulmonary function over a period of continued smoking, then the former could be used as a means of differentiating those who are more susceptible from those who are less so. Studies done on elderly bronchitic subjects have not shown such a relationship.\textsuperscript{86} However, this aspect of the problem has not been fully investigated in young smokers.

Thus, the present study was undertaken with the following objectives:
1. to detect the lung function changes, if any, with particular reference to small airways, in a homogeneous population of young asymptomatic smokers living in the same environment, and to delineate clearly the progressive changes which occur in the lung function of these same subjects with continued smoking.

2. to assess the limitation caused by these small airway changes in the maximal oxygen uptake of the subjects and

3. to study the immediate effects of tobacco smoking on the airways in order to determine the variations in individual susceptibility.

These three components of the investigation are presented in three separate sections. Section A deals with lung function changes in young asymptomatic smokers, the relationship of these changes to the intensity of smoking and the progressive changes which occur in smokers with continued smoking. The study of maximal oxygen uptake on these subjects is presented in Section B. Section C deals with the assessment of individual susceptibility, in terms of the immediate response to tobacco smoke. The last chapter sets out the general conclusions arrived at, and their significance.