

## THE PATHOGENESIS OF CHRONIC AIRFLOW OBSTRUCTION IN MAN

### Introduction

Our work is based on the hypothesis that subjects who develop chronic airflow limitation while smoking represent a susceptible minority of the total smoking population. This hypothesis is being tested on patients who present to the Thoracic Surgical Service of our Hospital with coin lesions. These patients are studied extensively in the pre-operative period and the information correlated with the structural data obtained from an analysis of the lung specimen obtained at operation. To date we have studied a total of 230 cases, most of whom have smoked heavily. The mean forced expiratory volume (FEV<sub>1</sub>) is greater than 80% of the predicted values with a normal distribution around the mean value. This shows that a large proportion of this population have normal airways function in spite of the fact that they have smoked heavily.

The specific ways that we intend to use the information to test the above hypothesis were stated in the application last year. The progress to date and the studies proposed for 1984-85 are outlined below.

### Progress - 1983-84

- (1) We have completed studies that show that mining and industrial exposure represents a risk to chronic airflow limitation over and above that due to smoking. This work will be presented at the American Thoracic Society in May, 1984 and a full manuscript has been submitted to the American Review of Respiratory Disease.
- (2) We have examined the morphologic and physiologic features of patients who have a clinical history of chronic bronchitis and compared them to patients who do not. These studies provide the first clear evidence that excess mucus production (i.e. chronic bronchitis) is due to inflammation of the central airways. Our previous work has shown that the airways obstruction is due to inflammation in the peripheral airways and studies completed in the past year show that there is no relationship between chronic bronchitis (i.e. excess mucus production) and airways obstruction (i.e. peripheral airways disease). Abstracts of this work will be presented at the American Thoracic Society in May, 1984 and at the Canadian Society for Clinical Investigation in September, 1984 (Appendices 1 and 2). Full manuscripts are in preparation and will be submitted to major journals within the next few months.
- (3) We have completed a study which shows that respiratory bronchiolitis can be detected by pulmonary function testing (Appendix 3). This puts us in a position to test for the presence of respiratory bronchiolitis and undertake a longitudinal study to determine

...../2

103543418

whether respiratory bronchiolitis is an early feature of chronic airflow obstruction.

Objectives for 1984-85

- (1) During 1984-85 we will continue to collect data that is designed to establish whether or not increased airways reactivity is more common in patients with severe airways obstruction. This work is based on the "Dutch hypothesis" (see original application) that postulates that severe airways obstruction occurs in the so-called asthmatic bronchitic. If this were true, measurements of airways reactivity could provide a useful way of selecting the susceptible minority of patients who are likely to develop severe airways obstruction as a result of smoking. We have presently studied bronchial reactivity in 40 patients who have gone for lung resection and will present preliminary data on these at the Canadian Society for Clinical Investigation in September, 1984. We believe that we will have to study about 100 cases in order to have sufficient data to test the hypothesis that increased airways reactivity is associated with the development of chronic airflow limitation.
- (2) We plan to pursue the question of where the site of increased permeability is in the airways of smokers. We first showed that animals (i.e. guinea pigs) exposed to cigarette smoke developed increased airways permeability and several laboratories, including our own, have shown that asymptomatic smokers have more permeable airways. We plan to place a combination of fluorescent tracers of differing size in the airways of the lungs removed at surgery in an attempt to determine whether the increased permeability occurs in airways with increased inflammation. If this were true, the measurement of airways permeability might provide objective evidence of the severity of the inflammatory disease in the airways.

Finally, we plan to begin studies of a population of office workers and a population of industrial exposed workers who are matched for age and smoking history. In this study we will use pulmonary function tests to establish the presence of the inflammatory process in the peripheral airways. When this has been done, we plan to follow these patients annually for a five-year period to determine whether or not the pulmonary function of those with peripheral airways inflammation will deteriorate at an accelerated rate compared to those who do not have this lesion. By carrying out this study in one group of office workers (British Columbia Hydro) and one group of industrial workers (Western Canada Steel Ltd.) we hope to be able to determine whether or not industrial exposure is an additional risk factor to the deterioration of airway function.

In summary, the budget request of \$88,402 for 1984-85 will allow us to continue to collect data that bears on the hypothesis that chronic airflow limitation occurs in only a susceptible minority of cigarette smokers. This request is exactly the same as outlined for this time period in the complete application submitted in 1983 (see Appendix 4 for budget details).

103543419