

**GRANT APPLICATION (1984-85) FROM THE MEAKINS-CHRISTIE
LABORATORIES TO THE CANADIAN TOBACCO MANUFACTURER'S COUNCIL**

The research we propose to undertake deals with fundamental investigations into the effects of diseases which are thought to be tobacco-related, namely chronic bronchitis and emphysema, on the respiratory system. Three inter-related aspects will be systematically studied.

1) **The function of the Respiratory Muscles in Chronic Obstructive Pulmonary Disease (COPD).** In recent years, it has become apparent that the work of breathing in patients with chronic bronchitis and emphysema may become so great that their inspiratory muscles become fatigued. Since such patients must continue to breathe 24 hours/day without rest, they may never get an opportunity to recover from fatigue. The situation is analogous to a marathon runner who must continue to run 24 hours a day for weeks on end. For these reasons we hypothesize that a substantial percentage of patients with chronic bronchitis and emphysema suffer from chronic inspiratory muscle fatigue and that this is a major contributing factor to their disability, i.e. their classic symptom of shortness of breath and their inability to exercise. We are applying to the Medical Research Council and to the U.S. National Institutes of Health to fund studies to determine if and how nocturnal ventilatory muscle rest may benefit the inspiratory muscles. We plan to measure the influence of this treatment on such basic properties of inspiratory muscles as strength, endurance and contractility. If this investigation is successful we will gain fundamental

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knowledge on the influence of chronic excessive loads on inspiratory muscle function. This is crucial to our understanding because there is no information in the literature on chronic overload of any muscle other than the heart. The literature on skeletal muscle fatigue deals virtually exclusively with fatigue that has been induced over periods of up to one hour. In dealing with fatigue that has been induced over weeks, months and years we are truly exploring an entirely new field where nothing is known.

Although we hope to attract funding from the MRC as of July 1, 1984, funding from the National Institutes of Health (if we are successful) will not start until the spring of 1985. In the meantime we must support a new member of Faculty - Dr. S. Newman - who will be involved in this project. We therefore request that the CTMC provide \$30,000 as salary support for him from July 1, 1984 to June 31, 1985.

2) Pathophysiology of Acute Respiratory Failure in COPD and its Treatment

Recent work in our Laboratory has shown that most of the generally accepted tenets concerning the pathophysiology of acute respiratory failure in COPD were wrong. Contrary to previous belief we have shown that in such patients the respiratory centers are not depressed but actually are hyperactive, leading to greatly increased activity of the respiratory muscles.

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Similarly, we have shown that administration of 100% O₂ is not dangerous because of the fact that it suppresses hypoxic respiratory drive but because it leads to impaired gas exchange within the lungs. The proposed research is designed to better characterize the factors leading to acute ventilatory failure in COPD patients and to improve their management during mechanical ventilation. Our approach is focussed on the fundamental role of intrinsic PEEP as an important determinant of respiratory failure and as a parameter which has to be taken into account during mechanical ventilation. By intrinsic PEEP (PEEP_i) we mean the positive end-expiratory pressure which is present in the lungs of these patients due to the fact that their expiratory flow is limited by airways obstruction. Our main hypothesis is as follows: Acute respiratory infection leads to rapid, shallow breathing with consequent pulmonary hyperinflation. This in turn leads to impaired function of the inspiratory muscles (diaphragm, etc.) and increased PEEP_i which in turn increases the work of breathing and decreases cardiac output. As a result the COPD patients require mechanical ventilation. Depending on ventilator setting, substantial PEEP_i may be present impinging on cardiac output. Hence PEEP_i needs to be minimized. This can only be done by on-line assessment of respiratory mechanics. We hence propose to apply a battery of non-invasive measurements of respiratory mechanics which we have recently developed for mechanically ventilated patients. In this connection it should be noted that these studies will not only allow a better management of the patients but (perhaps more

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important) also provide new a basic insight into respiratory mechanics.

For this research we request \$20,000 as salary to support Dr. Jason Bates who will design the computer programs required for the above on-line measurements of respiratory mechanics.

3) High Frequency Chest Wall Oscillation and Mucus Clearance.

High frequency chest wall oscillation (HFO/CW) is a method of great potential value in chest physiotherapy. Experiments on dogs have shown that it stimulates mucus clearance in both central and peripheral airways. It probably acts by a combination of direct action, via airflow interaction and reflex stimulation, via a parasympathetic pathway. We are currently studying the effects of HFO/CW on mucus clearance in human volunteers with normal pulmonary function, both smokers and non-smokers. This latter project will enable us to begin testing the method on patients with cystic fibrosis. We have received a grant from the Canadian Cystic Fibrosis Foundation for this study. In this application we propose two complementary lines of research for which we do not as yet have funding: a) To examine the effect of HFO/CW on patients with COPD. This study will follow the same general protocol as that involving CF patients, i.e. a single treatment first, and then a trial of repeated treatments for an extended period. We will monitor the effects with the aid of tests of small airway function, such as helium/air flow-volume curves and nitrogen washouts, as well as

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examining changes in sputum volume and quality. This study will be carried out at the Montreal Chest Hospital Centre. b) To study the effect of HFO/CW in dogs with elastase-induced emphysema. Dogs will be exposed to elastase in one lung only to induce unilateral parenchymal damage. We will then examine the response to HFO/CW, comparing the effects in the damaged side with those in the unaltered portion. We will look at tracheobronchial clearance and at the morphology of the lungs after sacrifice. This study should help to shed light on several basic questions - the relative role of airflow and reflex mechanisms in the stimulation of clearance, and efficacy/safety considerations in emphysema.

For this project we request \$20,000 for support of Dr. Marina Saetta who will be involved in this study. In addition, in order to complete the research on animal models in tobacco injury supported by the Canadian Tobacco Manufacturers Council in previous years, which is to be terminated by September 30, 1984, we request \$7,000 (plus 17% Benefits) as salary for the histology technician (Miss Elspeth Angus).

The above studies will involve considerable additional expenses, in particular an additional computer facility for data analysis and modelling and an oscilloscope needed for sputum analysis at the Montreal Chest Hospital Center, for which we request an additional \$13,025. Thus, the total amount requested for the July 1984 to June 1985 period (including 10% McGill overhead) amounts to \$100,336.

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SUMMARY OF PROGRESS

Mucus hypersecretion and pulmonary function in dogs exposed to cigarette smoke.

A total of 10 dogs have been exposed to cigarette smoke for 8 to 10 months each. The analysis has been completed for 6 dogs; The final pulmonary function experiments on the remaining four will be made within the next month. Several points have become apparent at this stage. First of all, the most prominent alteration has been in the quantity of mucus secreted. The increase has been highly variable - from 2 times control to more than 10 times control, but hypersecretion has occurred in all 10 dogs studied. Secondly, associated with this hypersecretion has been a reduction in the sensitivity to aerosolized methacholine, seen in the first six dogs as well as in the intermediate results of the remaining four. The association with mucus hypersecretion rather than reduced smooth muscle sensitivity comes out of the fact that the response to infused methacholine has not changed consistently. Mucus linear velocity in the trachea, on the other hand, has not been significantly altered, suggesting that the airways have adapted to handle the increased mucus load. Parenchymal changes, as opposed to airway changes, have been less apparent thus far, with no significant alterations in elastic recoil, although some dogs have shown an increase in residual volume. We will explore whether those dogs that have developed functional alterations show morphological evidence of them, employing the techniques that we have developed in our studies of

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human smokers. We have already seen some indication from scanning electron microscopy that the smoking dogs have evidence of enlarged or coalesced alveolar fenestrae . This may be one of the earliest indices of parenchymal damage. (See attached Appendices).

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BUDGET DETAILS

Salaries:

Dr. Steven Newman	-	\$ 30,000.
Dr. Jason Bates	-	20,000.
Dr. Marina Saetta	-	20,000.
Miss E. Angus	-	7,000. +
17% Benefits	-	1,190.
Total: salaries:		78,190.

Equipment and Supplies:

1 IBM P.C, XT Unit with options	-	9,100.
1 Oscilloscope Model DSO - 4200	-	2,850.
9% P.S.T.	-	1,075.
Total: equipment	-	13,025.
10% McGill University Overhead	-	9,121.
GRAND TOTAL:	-	100,336.

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