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CYCLE ERGOMETER AND VOLUNTARY HYPERVENTILATION EXERCISES IN PATIENTS WITH CHRONIC AIRFLOW OBSTRUCTION.

DESIGN OF A RANDOMIZED CONTROLLED TRIAL

By

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ABSTRACT

A strategy to investigate the effect of two exercise modes upon patients with chronic airflow obstruction (CIAO) is developed. The difficulties in defining and diagnosing the various pathological entities covered by the umbrella term CIAO are discussed. Following a review of the published studies of endurance exercise in the before mentioned patient population a clinical problem is identified. Cycle ergometer exercise and voluntary hyperventilation were the two modalities chosen to be investigated. A 2\(^2\) factorial design is selected in order that both modalities may be efficiently studied, singly and in combination, with the inclusion of a placebo exercise group.

A statistical method is described for measuring agreement between two technicians conducting a test identifying the diagnostic inclusion criteria. An additional criterion for entry into the study will be inclusion of only those patients who are particularly likely to maintain the randomly assigned maneuver. This will be determined by the response to a pre-experimental sequence of three weekly test events carried out concurrent to a CIAO stabilization period. The intensity of the exercise will be established using a standardized progressive exercise test and a maximum sustained ventilatory capacity procedure. The choice of the three outcomes was based upon a more total definition of rehabilitation. The three primary outcomes are endurance as measured by both a twelve minute walking test and a progressive multistage treadmill test. The patients' perception of their social, emotional and
physical function in response to the exercise regimen is additionally measured using a health index questionnaire.
ACKNOWLEDGEMENTS

Dr. Charlie Goldsmith provided inspired instruction, enthusiasm for the project, and commitment that was exemplary and for which I am greatly appreciative.

Thanks is extended to the readers, Dr. Peter Tugwell and Dr. Norman Jones for their valuable recommendations, constructive criticism and encouragement.

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CHAPTER I

Introduction

In 1974 the American Thoracic Society sponsored a conference on the scientific basis of respiratory therapy. It was indicated in the published reports\textsuperscript{134} that many of the modalities of therapy for patients with CAD had been derived empirically without adequate controlled investigation of efficacy. This was stated as being unsatisfactory because firstly, it denied patients of therapy because of skepticism by their physicians, and secondly, it may have resulted in medical resources and personnel being expended needlessly on therapy less than beneficial. Reviewing studies in the English medical literature of North America and Europe on endurance exercise therapy in patients with CAD demonstrates the same paucity of studies using the methodological criteria recommended at the 1974 conference by both Higgins\textsuperscript{75} and Colton\textsuperscript{31} or by other authors.\textsuperscript{139} Mertens\textsuperscript{118} reported under-referral of patients with CAD to exercise therapy programmes and that this may be due to skepticism is supported by the literature. Seventeen studies investigating endurance exercise with and without using supplemental inspired oxygen were reviewed and only one\textsuperscript{111} had an appropriate control group. As new therapies arrive on the scene they may replace the old, or rather, just become additional to the old. Endurance exercise directed specifically at the ventilatory muscles additional to conventional limb endurance exercise was suggested\textsuperscript{15} as
the rehabilitation programme for a defined group of patients in a published abstract in 1980. Although the original intent of the abstract was without fault, only three reports of ventilatory muscle training in CAO have been published. All used an uncontrolled, before-after strategy with small sample sizes: 10, 3 and 6 patients respectively. Furthermore, there is evidence, albeit from a less than strongly designed study that both limb endurance exercise and ventilatory muscle endurance exercise have the same effect. This results in a difficult decision for the pulmonary clinician. Do I use the old therapy, the new therapy, both, or none?

The primary intent of this thesis is to describe an experimental strategy to answer the before mentioned question. Re-stated: to determine whether voluntary hyperventilation (the new) and cycle ergometer exercise (old), singularly or in combination influence the function of patients with CAO.

The experimental strategy described deals with efficacy of the two maneuvers as compared with effectiveness. In other words, do the maneuvers do more good then harm to patients who fully comply with the treatments? Can these maneuvers work?

Compared with: do the maneuvers do more good then harm to those patients to whom they are offered? The latter is concerned with the efficacy as well as the acceptance of the maneuver by the patients. The difference can be measured in terms of compliance.

The proposed study is also directed at confirming and extending the findings from intensive study of a small number of patients in un-
controlled settings. This sequence of clinical trials is consistent with that recommended by Gonnella. The target outcomes are remeasured at an end-point of eight weeks and thus the maneuvers are being evaluated over a short period of time. It is desirable at this particular phase of clinical trial to not evaluate the maneuvers in terms of long range effects, such as, number of exacerbations, frequency and length of hospitalisation, mortality or indeed the functional outcomes for this investigation over a one year or longer period until efficacy has been established. The long range questions would indeed be appropriate to ask and be studied for effectiveness and/or efficiency given that any one or more of the maneuvers demonstrate that they can work.

Of secondary intent is to describe an experimental model that can be utilized in rehabilitation to answer other questions. Much of rehabilitation is composed of multiple interventions, which can result in an increasing number of therapies employing a greater number of professional groups, resulting in a greater financial expenditure. Factorial designs would permit investigation of the therapies singly or in combination, concurrently. For example, sophisticated education packages, stress management and physical exercise are common constituents of chronic disease rehabilitation programmes. The whole package may, or may not, have been shown to be beneficial. However, it may have components that do not contribute to the total package outcome. This could be sorted out, allowing for measurement of interaction between or among the components using a factorial design.
CHAPTER II
Chronic Airflow Obstruction

2.1 Introduction
Chronic airflow obstruction (CAO)\textsuperscript{152} is a diffuse disorder of the peripheral or small airways of the lungs. This pulmonary disorder is commonly referred to by one of many acronyms used for a family of disorders, all characterized by airflow obstruction. Otherwise they demonstrate different pathological features, clinical symptoms, signs and prognoses. This thesis relates to two of the four disorders: chronic bronchitis and emphysema. Asthma and bronchiectasis are the other chronic airflow disorders and each of the four can co-exist or present mutually exclusive of each other.

2.2 Mortality, Morbidity and Economic Load
The increasing mortality trend in Canada from 1961 to 1973\textsuperscript{74} can be seen in Graph 2.1. Mortality counts fail to describe the total adverse effects of CAO. Death certificates and hospital discharge records with diagnostic labels such as pneumonia, heart failure or heart disease may be applied to patients whose primary condition was chronic airflow obstruction. This would imply that the CAO mortality counts are being underreported. It is probable that there has been an increase in the incidence of CAO but this could also be a result of increasing awareness, improved recognition and/or the changing of diagnostic criteria. Underreporting of emphysema using death certificates
Graph 2.1
Number of Deaths in Canada from Chronic Bronchitis and Emphysema
1961-1973
has been reported in the U.S.A. Respiratory disease represented the third or fourth major cause of death to Canadian males in 1971 in the age groups 15 to 59, 60 to 64, and 65 to 69. Coronary heart disease, lung cancer, gastro-intestinal cancer, and arteriosclerotic disease excluding cardiovascular accidents had higher mortality rates. In the United Kingdom in 1955 a total loss of 27 million days work was attributed to chronic bronchitis. This represented more than 10% of all episodes of absence of industry for that year. The United Kingdom continues to have the highest mortality rate from chronic bronchitis in the world. In 1973 the U.S. Department of National Health and Welfare reported chronic bronchitis and emphysema as affecting 231,000 subjects per year and resulting in more than 90 million dollars payment for disability per annum. United States further reported in 1977 that the social and economic annual load from CAO was; 1 billion dollars for direct cost of treatment, 3.8 billion dollars for cost due to morbidity and 900 million dollars for costs due to mortality.

2.3 Definitions and Diagnoses

Various groups have varied little in their stated definitions for the four 'obstructive disorders'.

2.3.1 Chronic bronchitis

Chronic bronchitis: defined by its most common clinical manifestation, recurrent excess mucous secretion in the bronchial tree.

"Chronic productive cough being present on most days for at least three months of the year and for at least two successive years."
2.3.2 Emphysema

Emphysema: defined in morphologic or anatomical terms indicating destruction of tissue. "A condition of the lung characterised by abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls." 2

2.3.3 Asthma

The definition of asthma has provided more difficulty for the official bodies. It has been defined as: "widespread narrowing of the bronchial airways which changes in severity over short periods of time, either spontaneously or under treatment, and is not due to cardiovascular disease." 25

2.3.4 Bronchiectasis

"A permanent abnormal dilation of one or more bronchi" 7 as a result of destruction of the elastic and muscular components of the bronchial wall. The pronounced clinical characteristic is copious expectoration of mucus which separates into three layers and is predominantly suppuration.

The definitions of 'airway obstruction' and the syndrome "chronic airflow obstruction" are couched in morphologic terms and this would indicate that they can only be recognized or differentiated during life with difficulty. However, the term CAO identifies the most significant effect of these conditions - difficulty in airflow. Substitute measurement by volume-time analysis of expiratory airflow has been recognized as the primary clinical method 149 for identifying and quantifying airflow obstruction. The spirometric obstructive pattern
Figure 2.2
Subdivisions of Lung Volume (Adult)

IRV - Inspiratory Reserve Volume
ERV - Expiratory Reserve Volume
RV - Residual Volume
VC - Vital Capacity
IC - Inspiratory Capacity
FRC - Functional Residual Capacity
$V_T$ - Tidal Volume
TLC - Total Lung Capacity
Figure 2.3

Volume-Time Analysis of Expiratory Airflow

Forced Vital Capacity (FVC)

Vital Capacity

Time (Seconds)

Volume (Liters)
Figure 2.4

Volume-Time Analysis of Expiratory Airflow
'Obstructive Pattern'

- Normal or Decreased FVC
- Decreased Maximum Expiratory Flow at One Second (FEV_{1.0})
- Decreased Maximum Expiratory Flow Ratio (\frac{FEV_{1.0}}{FVC} %)

Vital Capacity

Volume (litres)

Time (Seconds)
[Figure 2.3] alone is not sufficient to identify or label each of asthma, chronic bronchitis, emphysema, or bronchiectasis. Clinical history, signs and symptoms are required. However, inter-observer variation in the detection of physical signs of airway obstruction reflected on the chest wall and measured by a standard deviation agreement index lies almost exactly midway between 100% agreement and chance expectation \(^{64,146}\). Spirometry is not without being subject to measurement error\(^{51,61}\) and equipment, method of performance and standardization recommendations have now been clearly stated\(^{51}\).

2.4 Chronic Bronchitis

The definition of chronic bronchitis is clearly clinical rather than morphologic and as such is usually diagnosed using symptomatic criteria. Standardization of the diagnostic criteria, the quality and quantity of sputum, and the degree of dyspnea induced by activity have been assisted by the skilled administering of an established questionnaire\(^{48,79}\). Both inter- and intra-observer variations have been observed indicating that care is required. The basic pathologic abnormality of excess production of mucous in the bronchial airways\(^{108,136}\) in conjunction with cigarette smoking\(^{56,151}\) and atmospheric pollution\(^{19,56}\), interfere with the clearance mechanism of the respiratory tract, rendering it susceptible to bronchial infections\(^{56,109}\).

As a result of their data from the prospective study of English office workers, Fletcher, Peto, Tinker and Speizer\(^{56}\) suggested a new hypothesis on the pathogenesis of chronic airflow obstruction. They postulated that cigarette smoking and air pollution promote mucous hyper-
secretion, a condition which is usually reversible upon avoidance of exposure. Mucous hypersecretion increases susceptibility to the current chest illnesses, but neither is directly associated with airway narrowing. Chronic airflow obstruction is a progressive disorder which is a separate result of exposure to tobacco smoke and other pollutants, developing only in susceptible individuals. [Figure 2.5].

Little is known about the factors that determine which individuals will or will not react to cigarette smoking and air pollution by developing either or both hypersecretory and airway obstruction disorders. Increasing evidence indicates that susceptibility to both or either disorders may be familial. Laurell and Erikson report an association between chronic airflow obstruction and the hereditary deficiency of alpha_{1} antitrypsin; a serum protein believed to be essential to protection of the lung against destructive action of naturally occurring lysosome proteases. All forms of CAO have been reported in association with the homozygote of the autosomal recessive trait but the clinical and morphologic picture reported is primarily one of panacinar emphysema. The heterozygotes have variable levels of alpha_{1} antitrypsin but little is known of any increased susceptibility to CAO.

By its simple definition, chronic bronchitis would seem to be innocuous and in its simplest earlier form, the manifestations are often ignored by the affected individual - 'a smoker's cough'. This uncomplicated picture may reign for many years, but in others it may progress to a severe ventilatory airway defect with inadequate gas ex-
Figure 2.5

Natural Histories of the Obstructive and Hypersecretory Disorders

- Susceptible to obstructive lesions
- Progressive Airways Disease & Emphysema
- Increasing Obstruction to airflow (falling FEV₁₀)
  - Stops smoking
  - Progression arrested but not reversed
- Susceptible to both obstructive and hypersecretory lesions
- Inhalation of tobacco smoke and other air pollutants
- Susceptible to hypersecretory lesions

- Mucous gland hypertrophy
- Mucous hypersecretion chronic expectoration
  - Bronchial infections
  - Loss of time from work
  - Expectoration remits fewer infections
- Stops smoking
- Eventual disability
  - Respiratory failure, death
change, marked limitation of functional tolerance and subsequent death. The characteristically prominent feature of chronic productive cough early in a disease may not be accompanied by any functional impairment. It may exhibit abnormalities in any of a small group of pulmonary function tests claimed to be sensitive to patchy obstructive disease in the small peripheral airways\(^{106}\). Tests include demonstration of frequency dependence of pulmonary compliance\(^*\), and elevation of closing volume. It has not been demonstrated that such individuals, with change reflected in these tests, progress to respiratory failure or severe CAO.

In normal lungs 90% of the total resistance to airflow is located in the larger airways. A ten-fold increase of resistance to flow in small airways is required to double the total airways resistance\(^{78}\). Progression of the pathological changes in the small airways or involvement of the larger airways ultimately results in elevation of total resistance to pulmonary airways. It is only then that pulmonary function tests may demonstrate a slowing of the maximal expiratory flow and a reduced vital capacity with no change in the total lung capacity. Chronic bronchitis also results in an elevated residual volume, slightly elevated or normal functional residual capacity, and a reduction in the expiratory reserve volume. Severe ventilation-perfusion imbalance is claimed not to be uncommon in chronic bronchitis with physiologic shunting related to mild distribution of ventilation and a relatively well-

\(^*\) Compliance will be used in two different contexts within this thesis. The present context is that of a mechanical property of the respiratory system and will receive the subscript 'RS'. Definition: Compliance means distensibility, a measure of the ease with which a body may be deformed. It is defined as volume change in ml produced by pressure change in cms of water\(^{70}\).
preserved pulmonary blood flow distribution. Impaired gas mixing thus occurs with observation of hypoxaemia and hypercapnia. Whether hypercapnia is more prevalent in chronic bronchitis or emphysema has been the subject of much debate. It is probable that a positive correlation exists between FEV\textsubscript{1.0} value of less than 1 litre and hypercapnia regardless of the type of CAO\textsuperscript{21,99}. Whereas chronic bronchitis is defined in clinical terms but does have morphologic correlates, pulmonary emphysema is defined in morphologic terms but can be recognized by clinical manifestations.

2.5 **Emphysema**

Two forms of this condition exist. Both diffusely involve the lungs so as to result in severely disturbed respiratory function and disability. The derivation of the two forms, centrilobular and panlobular is from the different distribution of the morphologic changes within the lung units. Centrilobular emphysema: a dilation is confined to the centre of the secondary lobules served by the terminal bronchioles. Panlobular emphysema involves more diffusely the lobule, with dilatation of the groups of alveoli distal to the distended bronchiole. Centrilobular emphysema has been reported\textsuperscript{104} to be associated with chronic bronchitis based upon histological examination of the bronchi. However, other reports have indicated that no difference exists in the clinical presentation\textsuperscript{18,153}.

The predominant symptom and earliest to appear is shortness of breath on exertion. Whether the patient presents with respiratory disability and restriction of normal activities of their living, or only
Table 2.1

Differentiation of Chronic Bronchitis and Emphysema

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>CHRONIC BRONCHITIS</th>
<th>EMPHYSEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predominant symptom-</td>
<td>May be absent or develop late in course</td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>Early - predominant symptom</td>
</tr>
<tr>
<td>PRODUCTIVE COUGH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early - absent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late - severe in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>advanced cases</td>
<td></td>
</tr>
<tr>
<td>SHORTNESS OF BREATH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usual</td>
<td></td>
</tr>
<tr>
<td>SMOKE HISTORY</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rarely</td>
<td></td>
</tr>
<tr>
<td>WEIGHT LOSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
<td></td>
</tr>
<tr>
<td>BARREL CHEST</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often in severely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>attacks</td>
<td></td>
</tr>
<tr>
<td>DECReased BREATH SOUNDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Signs of Cor Pulmonary</td>
<td>May be present in far advanced disease</td>
</tr>
<tr>
<td></td>
<td>Chronic Hypercarbia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperinflation</td>
<td>May be present</td>
</tr>
<tr>
<td></td>
<td>Flat Diaphragms</td>
<td>Frequently (diagnostic)</td>
</tr>
<tr>
<td></td>
<td>Increased Lung</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Markings</td>
<td></td>
</tr>
<tr>
<td>VITAL CAPACITY</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>RESIDUAL VOLUME</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>TOTAL LUNG CAPACITY</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>EXPIRATORY FLOW RATES</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>STATIC LUNG COMPLIANCE</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>DIFFUSING CAPACITY</td>
<td>Normal</td>
<td>Normal → Decreased</td>
</tr>
<tr>
<td>FUNCTIONAL RESIDUAL</td>
<td>May be increased</td>
<td>Increased</td>
</tr>
<tr>
<td>CAPACITY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
with mild awareness of dyspnea on heavy exertion is primarily dependent on the magnitude of work the subject engages in. This does not include a consideration of other iatrotropic stimuli that result in a patient seeking medical assistance.

During the early stages of emphysema the patient may have increased protection against hypoxia as compared with a patient with chronic bronchitis in that there is destruction of capillaries in the emphysematous part of the lung. This decreases perfusion in the areas of impaired ventilation thus maintaining a balance between them. Weight loss is commonly observed in emphysema which contrasts with the more normal body weight or obesity, given a similar degree of disability accompanying chronic bronchitis.

The chest may become hyperinflated, the lower ribs hardly moving, or moving inward rather than outward as a result of the narrow horizontal costal fibres of the 'flattened' diaphragm. The upper chest wall demonstrates increased movement with increased inspiratory contractile activity of the cervico-thoracic musculature.

The pulmonary function tests which have best identified the single entity of emphysema in its early stages are 'diffusing capacity' and 'lung recoil', both of which are reduced in emphysema but preserved in chronic bronchitis. Increased total lung capacity, residual volume, functional residual capacity and ratio of residual volume to total lung capacity all are more characteristic of emphysema than chronic bronchitis. Decreased vital capacity and maximal expiratory flow are also demonstrable in clinically identified emphysema.
The complexity of defining both chronic bronchitis and emphysema was demonstrated in a series of studies showing little difference existed between patients identified in London, England with chronic bronchitis and those in Chicago, Illinois diagnosed as having emphysema. The clinical and laboratory forms of CAO did not differ in the two countries, the major problem being one of semantics. It also attempted to separate out patients in whom airway obstruction was associated with emphysema from those with chronic bronchitis. It was suggested that a continuum existed; patients with extreme 'pure' emphysema and with no symptoms of bronchitis, to 'pure' bronchitis with no emphysema, through those patients who demonstrated emphysema and bronchitis. The 'pure' emphysematous patients were classified as Type A, bronchitic patients as Type B, and the indeterminate as Type X. Dornhorst is reported to have first classified CAO in terms of two syndromes: 'BB', the 'blue bloater', and 'PP', 'the pink puffer'. Many others have since used various terms to differentiate the syndromes, particularly 'BB' in slightly different descriptive ways. However, there appears general agreement that there are two syndromes, which might be called Type A and Type B. Type A patients have moderate to severe emphysema and Type B patients have a small amount of emphysema. Chronic bronchitis may or may not be present in either. If criteria are to be chosen to quantitate how much emphysema a patient may have, then the Burrows, Fletcher and co-workers criteria are the more specific.
### Table 2.2

Airway Reversibility in Asthma and Chronic Bronchitis

#### Asthma

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>BRONchodilator &amp; FEV&lt;sub&gt;1.0&lt;/sub&gt; Before</th>
<th>After</th>
<th>Litres</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.75</td>
<td>1.15</td>
<td>0.40</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>1.55</td>
<td>1.85</td>
<td>0.30</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>2.40</td>
<td>2.85</td>
<td>0.45</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>1.40</td>
<td>1.80</td>
<td>0.40</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>1.45</td>
<td>2.00</td>
<td>0.55</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>1.25</td>
<td>1.75</td>
<td>0.50</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>1.55</td>
<td>1.95</td>
<td>0.40</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>1.65</td>
<td>1.85</td>
<td>0.20</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>0.70</td>
<td>1.35</td>
<td>0.65</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>0.75</td>
<td>1.20</td>
<td>0.45</td>
<td>60</td>
</tr>
<tr>
<td><strong>X</strong></td>
<td><strong>1.35</strong></td>
<td><strong>1.78</strong></td>
<td><strong>0.43</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>

#### Chronic Bronchitis

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>FEV&lt;sub&gt;1.0&lt;/sub&gt; Before</th>
<th>After</th>
<th>Litres</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>0.90</td>
<td>-0.10</td>
<td>-10</td>
</tr>
<tr>
<td>2</td>
<td>.35</td>
<td>0.45</td>
<td>.10</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>1.15</td>
<td>1.25</td>
<td>0.10</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>.90</td>
<td>1.05</td>
<td>0.15</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>.55</td>
<td>.70</td>
<td>0.15</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>1.15</td>
<td>1.35</td>
<td>0.20</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>1.15</td>
<td>1.25</td>
<td>0.10</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>.75</td>
<td>.85</td>
<td>.10</td>
<td>13</td>
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<tr>
<td>9</td>
<td>.40</td>
<td>.55</td>
<td>.15</td>
<td>38</td>
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<tr>
<td>10</td>
<td>1.00</td>
<td>1.05</td>
<td>.05</td>
<td>0</td>
</tr>
<tr>
<td><strong>X</strong></td>
<td><strong>.84</strong></td>
<td><strong>.94</strong></td>
<td><strong>.10</strong></td>
<td><strong>12</strong></td>
</tr>
</tbody>
</table>
2.6 Asthma

The question being asked in this thesis precludes asthma primarily because of the reversible nature of the condition, but also because exercise is known to induce asthma\textsuperscript{135}. A definition of asthma overlaps chronic bronchitis, and furthermore, both are found to co-exist. Patients with chronic bronchitis may demonstrate a reversible component to the CAO without any clinical evidence of asthma\textsuperscript{145,150}. Using the FEV\textsubscript{1.0} as the measurement of airflow obstruction, the mean change in ten patients diagnosed as only having asthma was 32% [Table 2.2]\textsuperscript{145}. Given the same quantity of bronchodilator (200µg Salbutamol), ten patients diagnosed as having chronic bronchitis without asthma had a mean change of 12%. A change of greater than 30% is used as the cutoff point for identifying patients with asthma. However, this use of a percentage may penalize the patients with a very low FEV\textsubscript{1.0} (note patients 2, 5, 9, with chronic bronchitis, Table 2.2) and therefore it may be useful to have an additional exclusion criterion of less than .3 litres. Patients may develop asthma at the same time as they develop a chronic productive cough. It may also appear after chronic bronchitis has been diagnosed for many years. This situation has been termed 'chronic bronchitis with asthma'. Contraction of the smooth involuntary muscle of the bronchial wall (bronchospasm) is credited with playing a major role in the bronchooconstriction and airflow obstruction of asthma.

2.7 Bronchiectasis

A morphologic definition was stated earlier, but the clinical manifestation of voluminous quantities of purulent sputum which demar-
cates into three layers permits clinical recognition. The history is also characteristic, with episodes of pneumonia or pulmonary infection following childhood pertussis. The above mentioned clinical features tend to separate bronchiectasis from chronic bronchitis. In a clinical pathological study of patients with Type A and Type B CAO\textsuperscript{13}, patients with bronchiectasis were identified in each group, indicating that it co-exists with other members of the family or at least emphysema. The only definitive diagnostic method is bronchography which is instillation of liquid radiopaque contrast medium into the tracheobronchial tree and observing by fluoroscopic roentgenograms.

2.8 **Loss of Lung Function**

The forced expired volume in 1 second has also been used as the measure of establishing loss of lung function in subjects without CAO\textsuperscript{76} as well as patients with CAO\textsuperscript{17,46,56,81,86,115}. Four studies\textsuperscript{17,46,81,115} [Table 2.3] reported almost equivalent annual loss of FEV\textsubscript{1.0}, being between 82 ml/year and 88 ml/year in patients with CAO.

A loss of 82 ml/year was reported by Fletcher and co-workers\textsuperscript{56} only for the first five surveys during the first three years of their eight year survey. The population was of men without severe CAO in the early stages and who were in continuous full-time employment. This initial three year period was characterized by exceptionally severe winters for London, England. Repeated daily temperatures below 0°C were reported. However, these are conditions which would not probably be uncommon to the North American patient populations reported on by both Emirgil (-88 ml/year) and Burrow (-84 ml/year). Jones\textsuperscript{86} prospectively
Table 2.3

Loss of Lung Function

<table>
<thead>
<tr>
<th></th>
<th>Annual Loss FEV mls</th>
<th>Diagnosis</th>
<th>Population</th>
<th>Follow-Up</th>
<th>Mean Age of Sample</th>
<th>FEV Litres</th>
<th>'Other'</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC 113</td>
<td>FEV&lt;sub&gt;1.0&lt;/sub&gt;</td>
<td>Chronic Bronchitis</td>
<td>373 men</td>
<td>1-5 years</td>
<td>[40-59]</td>
<td>FEV 1.0 = 2.032</td>
<td>U.K. double blind multi-centre trial prospective</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td></td>
<td></td>
<td></td>
<td>50.3</td>
<td>FEV 1.0 &gt; 1.14</td>
<td></td>
</tr>
<tr>
<td>Howard 81</td>
<td>FEV 0.75</td>
<td>Chronic Bronchitis</td>
<td>112 men</td>
<td>7.1 years</td>
<td>60.7</td>
<td>FEV 0.75 = 1.2</td>
<td>U.K. prospective</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td></td>
<td>13 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emirgil 46</td>
<td>FEV 1.0</td>
<td>CAO MMEF&lt;1.84</td>
<td>91</td>
<td>6-13 years</td>
<td>59</td>
<td>FEV 1.0 = 1.48</td>
<td>U.S.A. - New York State Retrospective</td>
</tr>
<tr>
<td>Sobel</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burrows 17</td>
<td>FEV 1.0</td>
<td>CAO FEV&lt;sub&gt;1.0&lt;/sub&gt;&lt;sub&gt;&lt;60%&lt;/sub&gt; of predicted</td>
<td>171</td>
<td>1 year</td>
<td>59.1</td>
<td>FEV 1.0 = 1.00 ± .4 (sd)</td>
<td>U.S.A. - Chicago Prospective</td>
</tr>
<tr>
<td>Earle</td>
<td>84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
followed 100 CAO patients equally split between London, England and Chicago, Illinois over a period approximating three years. The patients were studied using the same standardized clinical and physiological techniques and were found to present similar clinical abnormality. The average decline in FEV$_{1.0}$ was 46 ml/year, being slightly greater in Chicago (53 ml/year) than in London (34 ml/year). This magnitude of loss is somewhat less than that reported in the first two phases but greater than the third phase of Fletcher's study.

During the third and final part of Fletcher's survey the decline in FEV$_{1.0}$ occurred with regular seasonal variation at 26 ml/year. This closely approximates the loss of 24 ml/year reported in a group of non-smoking British miners whose smoking colleagues had an annual loss of 52 ml/year. The overall change of FEV$_{1.0}$ in the Fletcher study was -30 ml/year. To Fletcher's credit, instrument error and observer variation were closely monitored and improvement in FEV$_{1.0}$ technique was identified during the second half of the study. They calculated the resulting underestimation of the loss in FEV$_{1.0}$ to be 10 to 20 ml/year. A number of sources of bias including those listed next, emphasize the danger of making comparisons across longitudinal studies.

1. Climatic differences including seasonal variation.

2. Different diagnostic criteria and changing criteria over time.

3. Different populations that vary both within and among in exposure to atmospheric pollution, industrial gases, and tobacco smoke.

4. Measuring instruments whose calibration and method of per-
formance is not reported or carried out.

5. Observer variation, including the number of observers and the degree of variation among them.

6. Changes in therapeutic management; different drugs, dosage and method of administration.

The overall rate of decline in ventilatory function measured by FEV$_{1.0}$ is difficult to determine. At the 'normal end' of the spectrum, measurement may include subjects with early undetected CAO which is not reflected in the FEV$_{1.0}$. At the other end of the spectrum, a very rapid deterioration, particularly in the patient with greatest impairment, is apt to result in death before the ventilatory changes are documented or reported.

It has been recommended$^{32}$ that the change in FEV$_{1.0}$ as a test of ventilatory function be considered in three phase. [Figure 2.6]. In the early phase of CAO, the condition 'smoulders' in the small peripheral airways with little or no change (probably less than 24 ml/year). The second phase demonstrates a more rapidly declining stage with a larger annual loss (probably between 30 ml and 82 ml/year). This will be a sensitive index of CAO until the FEV$_{1.0}$ falls below 0.75 litres. Substantial change may occur in the pathologic process during the third phase with little change in the FEV$_{1.0}$. Patients may then survive for as long as a decade without demonstrating a further decline in their FEV$_{1.0}$.
Figure 2.6
Progressive Loss of FEV$_{1.0}$ in CAO
CHAPTER III

Endurance Exercise Training

3.1 Introduction

The functional capacity of the biological systems of the human are able to develop an adaptive increase in capacity in response to increased stimuli or workloads, and can undergo a decrease in functional capacity when subjected to inactivity. The musculoskeletal and cardio-pulmonary systems have clearly demonstrated this. Bone mass loss (deosification, or bone atrophy) occurs when mechanical stimuli are reduced by immobilization, paralysis of the limbs or weightlessness. In the lower limbs the weight-bearing stress is the stimulus absent. The re-development process of the bony skeleton is described by Bassett re-stating Wolff's Law which dates back to the 19th century: 'the form of a bone being given, the bone elements place or displace themselves in the direction of functional forces and increase or decrease their mass to reflect the amount of the functional forces'.

The effects of bed rest on healthy young adults, as it affects the limb muscles and oxygen transport was reported upon by Saltin. Following twenty days bed rest, the oxidative capacity of skeletal muscles was decreased, as was the maximum oxygen uptake. The latter increased 30% greater than the pre-bed rest values after a fifty-five days running programme.

Many of the usual activities of daily living do not test the
muscular, respiratory or circulatory systems to their maximum. Therefore, symptoms relating to a decrease in functional capacity of the physiological system may only be experienced when the loss has been substantial. The relationship that exists between clinical symptoms and the severity of the underlying function derangement has been described by Jones as being non-linear. (Figure 3.1). The patient with symptomatic CAO and a markedly reduced ventilatory capacity is probably operating on the more vertical component of this curve. A small loss in physiological capacity will result in a relatively large loss in ability to function. However, the ability of the patient to carry out daily activities is not solely confined to loss of capacity in physiological terms. The pulmonary patients referred for rehabilitation have been described as frightened by their shortness of breath and depressed. They will avoid any activity that may result in shortness of breath. Thus, such a patient's functional capacity or ability to perform daily activities is on a downward spiral:

breathlessness
\[\downarrow\]
fear
\[\downarrow\]
less activity
\[\downarrow\]
deconditioning
\[\downarrow\]
increased breathlessness with same workload
\[\downarrow\]
fear...
Figure 3.1

Physiological Capacity %

Ability to perform daily activities
In defence of an argument for manoeuvres attempting to halt or slow down this disabling pattern of events and increase the function of patients with CAO, we can return to Figure 3.1. On the steep part of the curve it can be postulated that the corollary of small loss of physical capacity and large loss of activities of daily living may be that a small gain in physical capacity will result in a large gain in daily living activities.

Various physical therapeutic manoeuvres have been employed to this end and fall into three broad categories:

1. manoeuvres aimed at clearing secretions from the bronchial tree;
2. the learning of chest and abdominal wall movements which are in turn directed at:
   (a) decreasing breathing rate and increasing tidal volume,
   (b) increasing diaphragmatic movement,
   (c) decreasing upper intercostal and other accessory muscle activity to improve efficiency,
   (d) improved activity tolerance;
3. endurance exercise training directed at increasing the capacity for aerobic work.

The latter is of primary concern in this thesis, but it is worth noting that both of the other categories may be very much influenced by the third. The increased tidal volumes incurred in exercise particularly if occurring at high lung volumes could effect clearance of secretions. Additionally, if not negatively, endurance exercise training in
the midst of a polluted environment will result in much of the inspired ventilation bypassing the built-in physiological filter of the nose. This will result in an increase in airway exposure to an irritant likely to cause hypersecretion\(^{128}\). The overlap with learning of kinematic patterns will be mentioned later in this chapter.

The studies I have reported on in this chapter have used treadmill\(^{120,124,125,131,132}\) and cycle ergometers\(^{1,9,42,100,156}\) as the training modes as well as calisthenics\(^{24}\), walking and jogging\(^{118}\), stairs\(^{111}\) and recreational activities\(^{94}\). A relatively newer group of studies investigating endurance training of the ventilatory muscles will also be reviewed. The possible mechanisms involved in effecting improvement in function will be discussed, and finally in this chapter, the rationale for the proposed study will be stated.

3.2 Cycle Ergometer Studies

Five studies using a cycle ergometer for training are described next and summarized in Table 3.1.

Vyas\(^{156}\) applied a 'before and after' strategy to fourteen CAO patients all with \(\text{FEV}_1.0\) less than 1.51 litres. Three of the patients were unable to complete the programme of duration varying between 5.8 and 25.7 weeks. Ninety per cent of the maximal load calculated from a progressive cycle exercise test was the intensity of the interval training of duration one to two minutes. The major changes reported were a decreased ventilation at a comparable submaximal workload without a change in heart rate, oxygen consumption or carbon dioxide production. The total work capacity was increased as was the total oxygen consump-
<table>
<thead>
<tr>
<th></th>
<th>Vyas^156</th>
<th>Bass^9 / Alpert^1</th>
<th>Laros^100</th>
<th>Degre^42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy</strong></td>
<td>Before-After</td>
<td>Before-After</td>
<td>Before-After</td>
<td>RCT</td>
</tr>
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<td><strong>Sample Size</strong></td>
<td>14</td>
<td>12/4</td>
<td>?</td>
<td>30</td>
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<tr>
<td><strong>Test Device</strong></td>
<td>Cycle</td>
<td>Cycle (Diary)</td>
<td>Cycle</td>
<td>Cycle</td>
</tr>
<tr>
<td><strong>Test Instrument</strong></td>
<td>Cycle</td>
<td>Cycle</td>
<td>Cycle</td>
<td>Cycle</td>
</tr>
<tr>
<td><strong>Training Pattern</strong></td>
<td>Interval 90% Maximum 1-2 Minutes ×5 per Week</td>
<td>Continuous 18 Weeks 3 × Each Day</td>
<td>&lt;40% Maximum Interval – Modified ×4 per Week for 4 months</td>
<td>3 × per Week × 6 Weeks 25' at 75% Maximum with 3-4 litres supplemental oxygen</td>
</tr>
<tr>
<td><strong>Co-Intervention</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>3 Dropouts Attendance?</td>
<td>1 Dropout Attendance?</td>
<td>?</td>
<td>14 Dropouts</td>
</tr>
<tr>
<td><strong>Selection</strong></td>
<td>FEV&lt;sub&gt;1.0&lt;/sub&gt; &lt; 1.5</td>
<td>'High Motivation' inclusion criteria</td>
<td>No cardiac involvement. Emphysema only</td>
<td>'Moderate to Severe' CAO, no cardiac dysfunction. 6/52 stability of CAO</td>
</tr>
<tr>
<td><strong>'Findings'</strong></td>
<td>↑ Work Capacity ↑&lt;sub&gt;V&lt;sub&gt;M&lt;/sub&gt;&lt;/sub&gt; Submax Load ↑&lt;sub&gt;VO&lt;sub&gt;2&lt;/sub&gt;-L&lt;/sub&gt; 3 patients – No change</td>
<td>↑F rest and exercise ↑Daily activities ↑Work capacity</td>
<td>↑Well being 'possible' ↑&lt;sub&gt;V&lt;sub&gt;M&lt;/sub&gt;&lt;/sub&gt; at Submaximal load</td>
<td>Exercise Group ↑Resting &lt;sub&gt;P&lt;sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;&lt;/sub&gt; ↑&lt;sub&gt;VO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;-L Control Group ↑&lt;sub&gt;V&lt;sub&gt;M&lt;/sub&gt;&lt;/sub&gt; &lt;sub&gt;FaO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;</td>
</tr>
</tbody>
</table>
tion and CO₂ production. The symptom-limited maximum oxygen consumption increased by 10% but no claim of increased efficiency at a submaximal load was made. The most likely explanation for the increased work capacity and corresponding increase in oxygen uptake being a positive change in motivation. However, the important issue is that for all but three patients who made no change, more work was completed, thus permitting the patient to possibly perform more daily tasks.

An uncontrolled home cycle exercise programme was evaluated by Bass using a six minute cycle exercise test and daily diary. The diary included a pedometer reading, exercise duration, cycle tension and comments. A baseline was established followed an habituation period in hospital for one week. After eighteen weeks of exercise the remaining eleven patients all demonstrated an increased work capacity and an increase in activities of daily living as recorded by the diary. Maximum voluntary ventilation was also increased. A change in cardiovascular function was reported with a reduction in heart rate at rest and also during the fifth minute of the exercise test. Five of the aforementioned eleven patients are further reported on by Alpert after volunteering to undergo further haemodynamic and pulmonary function testing. No improvement in cardiac or pulmonary function was observed and Alpert and his coworkers thought that the increased tolerance was probably a result of greater efficiency of exercising limb and/or respiratory muscles.

In Holland, Laros used a different approach to endurance exercise. He was concerned that a high intensity of activity and exercise
might result in overstretching of the lung parenchyma. Therefore, cycle exercise was limited to less than 40% of the highest attainable performance. This was prescribed from a three minute exercise test which had nonspecific subjective endpoints. A symptomatic gain of improved well being was reported as was a decreased resting heart rate and increased tidal volume, but no data collection was discussed. The patients exposed to the exercise were only those who were 'fighters, pink and puffing and emphysematous'. The major differentiating criterion was the absence of cardiac involvement. No adverse effects were reported.

Also in Europe, Degre attempted a randomized controlled clinical study but analyzed the data in a 'before-after' nature. The probable reason being, that only five of the initial fifteen control patients did not drop out from the programme. Four of the exercise group dropped out. The loss in the control group may have been partly the result of receiving the control therapy for an extended period of time. All of the initial pre-randomized sample received the control therapy [breathing exercise] for six weeks prior to the study period during which time it was established that their airway obstruction was stable. Both training and testing was performed on a cycle ergometer. An additional aspect of this study was the provision of supplemental oxygen therapy (3-4 l/minute) only to the exercise study group. This was provided in neither a single or double-blind manner. A right-heart catheterisation at rest and exercise was also carried out. Analysis of the resting pulmonary artery pressure which probably was a result of the oxygen therapy.
oxygen therapy. The resting arterial oxygen tension also increased but no changes were noted at comparable submaximal workloads and a symptom-limited oxygen uptake increased by 10% as was found by Vyas. The five patients in the control group did not demonstrate an increased symptom-limited maximum oxygen uptake but their total ventilation did increase over the duration of the study.

3.3 Summary

Other cycle ergometer training studies using supplemental inspired oxygen have not been reviewed. Cotes\(^{38}\) has made recommendations for deciding upon the use of supplemental oxygen. Similarly, complex rehabilitation studies with multiple therapies have not been reviewed.

Five exercise studies in the literature have been reported upon using four small patient populations. Only Degre attempted to use a control group but did not control for the oxygen therapy. Laros described a multiple therapy rehabilitation programme using a considerably lower intensity of cycle exercise of which the benefits accrued cannot be attributed to any one of the therapies. Vyas, Bass, and Degre prescribed exercise from a standardized laboratory exercise test. Bass and Vyas allowed for the habituation effect. All the studies reported, used the same device for testing and training which resulted in a stated improvement in working capacity. This may explain the increased working capacity without any or much change in physiological variables. However, mechanical efficiency, or the reduction of unnecessary movement may have occurred, possibly permitting better utilization of the same oxygen supply. This implies that the modified measurement of
aerobic capacity, symptom-limited maximum oxygen uptake as described by Degre, is more difficult to interpret than in healthy subjects. For example, any variable that brings about either a decrease in anxiety or dyspnea, or improves motivation, will result in an increased workload or work duration, thus permitting a new and higher oxygen uptake measure.

Bass was the only author who reported use of a functional everyday activity outcome - a daily diary. Maybe the result of change in life styles would have been more useful if measurement had been initiated prior to the habituation period. It is possible that the hospitalization and the habituation period also effect a change in life style. A diary does seem to be a useful incentive instrument for the patients.

Many of the issues identified will be further developed in the following sections of this chapter.

3.4 Treadmill Exercise Studies

The following treadmill studies are summarized in Table 3.2.

Miller briefly described the effects of six weeks exercise with supplemental inspired oxygen of 40% in three patients. An increased work capacity was reported with an increase in maximum ventilation and symptom-limited oxygen uptake. A reduction in respiratory rate, heart rate, and oxygen consumption at a submaximal workload was also documented. A subjective gain on working maximally for 2.5 minutes was an "increased comfort during physical activity and greater physical independence". Improved efficiency of performance was claimed based on the gains at a submaximal workload.
<table>
<thead>
<tr>
<th></th>
<th>Miller 119</th>
<th>Nicholas 124</th>
<th>Pierce 132</th>
<th>Paerz 126</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy</strong></td>
<td>Descriptive</td>
<td>Before-After</td>
<td>Before-After</td>
<td>Before-After</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>7-3 reported</td>
<td>15(8)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td><strong>Test Device</strong></td>
<td>Treadmill with and without ( \text{O}_2 )</td>
<td>Treadmill</td>
<td>Treadmill</td>
<td>Treadmill and Cycle</td>
</tr>
<tr>
<td><strong>Training Device</strong></td>
<td>Treadmill</td>
<td>Treadmill</td>
<td>Treadmill</td>
<td>Treadmill</td>
</tr>
<tr>
<td><strong>Training Pattern</strong></td>
<td>6 weeks 1-2 daily 2-5 minutes maximum tolerated</td>
<td>6 months 3 walks per session 3x per week</td>
<td>Ranging from 3 to 20 weeks 2-5 minutes 5 to 10 times daily submaximal</td>
<td>21 days 5x Each Day for 10’</td>
</tr>
<tr>
<td><strong>Co-intervention</strong></td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>Probably</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Selection</strong></td>
<td>CAO</td>
<td>Exertional dyspnea, 'physical signs' of hypoxia, fatigue and exercise obstruction</td>
<td>Severe 'obstructive', excluding of marked cyanosis. LVT ventricle dysfunction, arrhythmias</td>
<td>Emphysema, Hypoxemia, dyspnea on walking 3’</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>+Work Capacity +HR at Submaximum +RR at Submaximum +( \text{VO}_2 ) +( \text{V} ) Total +( \text{VO}_2 ) S-L</td>
<td>+Walking Tolerance during control and exercise periods</td>
<td>+Walking Tolerance Submax x Load +HR +RR +V + M +O(_2) consumption +CO(_2) production +Post exercise recovery time</td>
<td>+Stride Length +Cycle +( \text{O}_2) consumption +( \text{a-vo}_2) difference</td>
</tr>
</tbody>
</table>
Pierce\textsuperscript{131} exercised on a treadmill four patients who demonstrated marked hypoxia (PaO$_2$=31mmHg) or multiple ventricular premature contractions on exercise. They received supplemental oxygen during exercise. The four patients showed reduction in respiratory rate, maximum ventilation, oxygen consumption and CO$_2$ production when breathing air at a submaximal workload following training. The same author also reported\textsuperscript{132} on the effects of treadmill exercise on the remainder of his CAO population. Similar gains were again reported. Further gains were decrease in heart rate and a larger gain in both respiratory rate and ventilation at a submaximal level of work. These results indicate that an increase in mechanical efficiency may occur with repetition of an exercise level, which in turn leads to an increased activity tolerance. This supports the previously discussed mechanism of more efficient use of an unchanged oxygen reserve.

Nicholas\textsuperscript{124} in an attempt to submit fifteen patients to a prolonged habituation period of three months prior to an endurance exercise programme of six months duration, reported some interesting results if not problems. Only eight patients completed the nine months study. Three of the eight patients increased their walking score during the six month experimental period in contrast with five of the eight patients who increased their walking score during the control period. Seven of the eight patients showed an overall increase in walking score throughout the nine months. Of the three who improved during the second phase of the study, two only gained immediately following a course of steroid therapy in hospital or following an episode of 'flu'.
The intent of the initial three month period was to permit the patient to become familiar with treadmill walking and this is probably what did occur. The frequency of exposure to the treadmill was once a week during the three month habituation period, and three times a week during the experimental phase, plus an increased intensity and duration per session. That mechanical efficiency or task learning was probably effected through an habituation procedure is supported by the observations of Nicholas. The patients were described on entry into the study as being "tense, tight, and fearful of exertion and dyspnea". Following exposure to the treadmill, changes in their gait were noted, namely longer steps and co-ordinating their breathing and leg movements. However, other aspects of habituation could also result in increased activity. A decrease in anxiety and a change in life style may also have played a large role in this study, especially considering the frequency and dosage of the treadmill exercise in the early phase. This argument may be strengthened by the results of one subject (A.K.), who withdrew from the study after the initial three months and was re-evaluated at the end of the six month exercise period, without any formal exercise or change in medical therapy in the interim. His walking score and symptom-limited oxygen uptake were increased, being equal to, and greater than, three of the remaining patients. Social service interviews which questioned on daily living activities could have been useful here. Unfortunately these were carried out only once at the end of the study, the results therefore being dependent upon recall over six of nine months. Six of the eight patients indicated that they had
improved overall, being able to carry out more household tasks. The fluctuation in walking scores and maximum oxygen uptake during the second phase may have been the result of irregular attendance, exacerbation of airway obstruction, changes in emotional status and variability in the measurement itself.

Changes in gait on a treadmill were also observed by Paez, who noted a progressive increase in length of stride regardless of whether patients walked with or without supplemental oxygen. The mean increase in stride length was 23% and was accompanied by a decrease in heart rate and minute volume at a submaximal load. The patients' gait was seen to have a less marked forward stoop and less stiff legs. That this gain was task-specific was demonstrated by additional testing on a cycle ergometer. No cardiac or pulmonary function improvement occurred and no gain in endurance or symptom-limited oxygen uptake was measured.

3.5 General Activity Studies

Three studies, using everyday type activity as a mode of exercise, each from a different continent: Australia, Europe (Scotland) and North America (Toronto) are discussed next.

Christie exercised eleven male patients with severe CAO (less than 1 litre) with a programme of fifteen minutes exercise for two weeks. Exercise consisted of multiple repetition of four calisthenic exercises, five minutes stepping exercise and a walk of between .5 and 1.0 mile. One patient died from a mild cardiac infarction and nine of the ten subjectively reported considerable improvement in wellbeing and exercise tolerance. Higher maximum workloads were performed at higher
respiratory minute volumes which may reflect an increased willingness to tolerate dyspnea. Lower respiratory minute volumes per unit of work were also found at a submaximal load. Christie claims his trial to be an own-control strategy but the number of exercise tests stated and the description of the analysis suggests that this is a before-after study with a stabilization period.

McCavin reported a controlled trial of unsupervised home exercise which consisted of stair climbing recorded by a diary. The control group received no instructions but were followed up at the same intervals as the exercise group. Random assignment to the groups was claimed but it is difficult to concur with this claim. The author reported twenty-eight patients were initially studied but that four dropped out of the exercise programme group. However, twelve patients for each of the two groups were reported on in the analysis. The analysis itself failed to be complete in that the before-after differences in each group were not compared. Increased exercise tolerance was observed using a twelve-minute walk test and a progressive cycle exercise test. Decreased breathlessness, increased wellbeing and improved cough and sputum volume were subjectively attained. Improvement in general activities was perceived to have occurred as reported by the patients. The maximum workload was increased without a change in symptom-limited oxygen uptake or oxygen consumption at a submaximal load. No change in ventilation occurred either. The increase in twelve minute walking also demonstrated an increase in length of stride, suggesting increased efficiency in gait.
Of the four patients lost to the study, one died of infective exacerbation of CAO and one dropped out as a result of depressive illness. An interesting observation in this study was a difference in mean illness days per subject between the groups. The exercise group reported ten days illness per subject contrasting with one day's illness per subject in the control group. It can be speculated that this is a result of the examining physician taking greater care or looking more closely for illness in one group of patients. Alternatively, it may be related to the exercise programme regimen itself. Single-blindness is frequently considered as the patient being blind, but it would be useful to also blind the examining physicians. The patient may, on repeated daily exposure to increased activity, become more aware of their dyspnea. One response to this may be that they become preoccupied with the symptom and adopt the 'sick role'. Both Christie and McGavin indicated that patients with an exacerbation of their illness during the study were treated by conventional drug therapy and retained in the study. The effect of this change in management, not equal between the groups, could influence the results of the trial. Patients in Nicholas' study improved their walking tolerance markedly immediately following drug therapy during the study period.

In Toronto, Mertens ran a weekly programme of walking and jogging for thirteen CAO patients for one year, six of whom continued for a further year. Following exercise tests at six month intervals, eight patients reported varied subjective gains. Five of the eight reported perceived increase in exercise tolerance and six a decreased
number of infections. Five patients did not improve or deteriorated. Three of these failed to exercise regularly, one exercised without improvement, and the other was reported as having lost weight, being depressed, more disabled, and finally, stopped exercising. Objective gains in endurance of the quadriceps muscles, decreased heart rate at submaximal workloads and a widening of the arterio-venous oxygen difference would suggest that change at the muscle and oxygen transport level contributed to the increased work capacity.

That arm or leg exercise may result in an improvement in ventilatory muscle endurance performance was the subject of a 1980 published abstract. Three patients exercised their legs and four patients their arms, four days a week for six weeks. All patients had moderate to severe CAO (FEV₁ < 1.04 litres) and both groups had an increased ventilatory muscle endurance measured over fifteen minutes on completion of the exercise programme. This introduces a possible new mechanism to help explain the improved performance in response to exercise training programmes.

3.6 Ventilatory Muscle Endurance Training

Leith and Bradley in a controlled study, defined ventilatory muscle endurance as the time to exhaustion during partial re-breathing in a circuit which permitted regulation of oxygen and carbon dioxide levels. Exhaustion was defined as being unable to keep up with a target level of ventilation. Four healthy adults trained such, daily for five weeks and were compared against five adult controls who performed no such exercise. Endurance training was associated with an increased
sustained ventilation when compared against a control group (19% gain over 15 minutes). No change in vital capacity resulted. The importance of these published results were increased in the light of the study by Roussos and Macklem\textsuperscript{138} which led them to believe that the ventilatory muscles could become fatigued. A muscle’s endurance capacity is correlated with its resistance to fatigue. Therefore, further protection against fatigue may be afforded by increasing the endurance capacity of the respiratory muscles. Holloszy\textsuperscript{80} has demonstrated that muscles, which have adapted to increased loads by increasing the oxidative capacity, appear to be more resistant to fatigue. Similar results were found in two of the major muscles of walking (gastrocnemius and quadriceps) in rats\textsuperscript{7}. All three types of muscle fibres increased their oxidative capacity. This has been further supported at the animal level by demonstration of adaptation of the guinea pigs diaphragm in response to endurance training on a treadmill\textsuperscript{105}. This resulted in an increased proportion of high oxidative muscle fibres. That the adaptation at the cellular level of the respiratory muscles in rodents in response to exercise loads may also occur in response to a chronic respiratory load was examined by Keens\textsuperscript{93}. In a five week contral trial using thirty-five rats, fifteen of which were banded around the trachea, he found an increased oxidative capacity greater in the diaphragm than in the internal intercostals. The possibility of a change in the utilization pattern of the different fibre types in the diaphragm was also raised with greater use and hypertrophy of the slow twitch, high oxidative fibres. The internal intercostals also showed the capacity to increase their
oxidative capacities in order to compensate for experimental loss of neural drive to the diaphragm in rabbits and cats. This is not entirely analogous with the changes in the respiratory system of the patient with CAO in that the neural drive is intact, if not increased. However, the position of the diaphragm in the patient with CAO may be such (low, flat) that based on an ideal length-tension curve, the foreshortened fibres of the diaphragm may not be able to produce much positive muscle work. The internal intercostals and other inspiratory accessory muscles then become the primary drivers of inspiration. Furthermore, it is probable that the internal intercostals have only approximately half the oxidative capacity of the diaphragm and therefore may fatigue more readily. Summarizing the reports at the animal level of study, it is suggested that the limb and ventilatory muscles adapt to changes in functional demands imposed upon them by increasing the oxidative capacity of the muscle fibres.

Without inferring causation at the human level from animal experiments, it can be suggested that the documented changes within the muscle in response to exercise, enhance the mechanical efficiency and skill development mechanisms claimed in the clinical cycle and treadmill exercise studies. It could also be postulated that some of the gain in the exercise studies was the result of training the respiratory muscles but no measure of respiratory muscle endurance or pattern of breathing were documented. In the last few years, a number of studies and reports have been published pertaining to improving endurance capacity of the whole body in response to ventilatory muscle endurance train-
ing. These studies will now be discussed.

Eleven teenagers with Cystic fibrosis were exposed to one of two exercise programmes for four weeks at a summer camp. Four non-random allocation treatment groups were described. Four Cystic fibrosis subjects exercised their ventilatory muscles using a partial re-breathing circuit for one fifteen minute run daily for four weeks. Seven Cystic fibrosis subjects participated in a four week physical activity programme which consisted of at least 1.5 hours each day of swimming and canoeing. However, the group with Cystic fibrosis on the ventilatory muscle training circuit also had an increase in their physical activity, albeit less than the other group. The author also used two non-concurrent exercise groups which consisted of 'normal', healthy adults. Four adults trained their ventilatory muscles at a different dosage from the Cystic fibrosis children and seven adults who were called the control group did nothing for four weeks. No pulmonary function gains resulted over the study period. Both the Cystic fibrosis group improved their ventilatory muscle endurance. The normal adult control group did not gain in ventilatory muscle endurance while the other adult group did but to a lesser degree than the Cystic fibrosis children. Whether or not the increased ventilatory muscle endurance resulted in an increased ability to exercise and do daily tasks is not discussed. However, it is claimed that upper body endurance exercise is equally effective at increasing ventilatory muscle endurance as specific training of these same muscles.

Belman, in an uncontrolled trial published in 1980, claimed
that ventilatory muscle training improved exercise capacity in ten patients with CAO. A re-breathing circuit similar to that used by Keens was used. The patients had two daily exercise runs of fifty minutes each for six weeks. The work capacity on the training circuit was increased but no change in oxygen consumption, heart rate or lactate production occurred at a level comparable with a pre-training maximum level of work. However, in contrast with Paez and coworkers in their treadmill and cycle exercise study, improvement was not task-specific. Gains were demonstrated in both arm and leg submaximal endurance tests as well as a twelve minute walk test. It was further claimed that the mechanism behind the change was neither a result of a learning effect or improved efficiency of breathing which the writers supported by the absence of change in variables measured at comparable submaximal levels of ventilatory endurance work. A change in pattern of breathing was also claimed in that the tidal volume increased in the presence of an unchanging breathing frequency.

Fanta studied three patients with CAO and concurred with Belman in that ventilatory muscle endurance training can increase the aerobic performance. However, Fanta also claimed increased efficiency of ventilatory muscle performance based on a lower oxygen consumption at a comparable submaximal level of hyperpnea. This occurred following six weeks of training for one hour a day, three times each week. Improved treadmill work was also demonstrated, supporting Belman's evidence that the training was not task-specific.

Peress reported on six patients with CAO following one month
of daily ventilatory muscle endurance training. Using the training device as an outcome, they reported an increased mean endurance capacity. Of particular note in this pilot study is that two of the six patients showed no change whatsoever in ventilatory endurance. It was suggested that the latter two patients were already fully trained prior to commencing the exercise programme.

3.7 Summary and Discussion of Mechanisms

A dearth of strongly designed clinical trials is rather obvious. However, it would appear impossible to design exercise studies that are double-blind in nature, and additionally, it is difficult to evaluate their effect. Drop-outs or non-compliance in long term rehabilitation studies is not rare. However, the major weaknesses in the before-after mentioned studies are solvable. For example, very small sample sizes and the absence of control groups can be overcome. When a control group was present, the choice was not always appropriate. There is little acknowledgement in the choice of outcomes that exercise and rehabilitation may be measured in terms of total health rather than laboratory testing of physical function. Quantification of the exercise programme was frequently not documented and single-blindness was rarely discussed.

On reviewing the literature, specific trends appear to have formed as a result of the exercise studies.

A. Endurance exercise directed at the lower limb or whole body may increase the aerobic work capacity in CAO patients.

B. Ventilatory muscle endurance exercise increased the aerobic work capacity in CAO patients.
C. Arm and leg exercise may improve the ventilatory muscle endurance capacity in CAO patients.

D. A. appears to be task-specific, whereas B. has transferable effects to other activities.

E. A number of mechanisms may be responsible for the increased aerobic capacity, and more than one may be operating at the same time.

3.7.1 Anxiety, Fear and Habituation

As a result of the increased contact and support of the medical staff, as well as the patient group interaction, a reduction in anxiety and fear of dyspnea may be effected as well as an increase in motivation and effort. Personality alterations in the form of the neurotic triad of somatic concern, depression, and conversion tendencies have been reported in dyspneic patients with CAO. Improvement was claimed following an exercise programme and this may have occurred through the process of counterconditioning or reciprocal inhibition as described by Wolpe. Improvement in performance by attention, support and group interaction would probably occur during the early phase of exposure to exercise. Counterconditioning, although probably requiring an initial low intensity of work, would be operative at gradually increasing levels of work and therefore over a longer duration of time. Just as exercise and repeated exposure to dyspnea may help patients tolerate greater degrees of breathlessness, it may be that repeated exposure makes the patient more aware and preoccupied by their symptom (a component of the neurotic triad), thus adopting a 'more sick role'. McGavin's study would support this. The patients who do not improve,
do not appear to demonstrate pre-exercise physiological function markedly different from those who do improve.

Habituation to repeated laboratory exercise tests resulting in a reduction in heart rate has been reported on by Davies[^40]. Most of the studies reported on here, permitted an habituation period. Reduction in anxiety may result in a change in life style and increased activities external to the formal exercise programme. This may also result in increasing aerobic capacity. This information is essential to any exercise study.

3.7.2 Task Learning

Improvement in performance may be the result of task learning. Frequent repetition of a movement pattern reduces extraneous body movements, producing better techniques and greater mechanical efficiency. In the presence of increasing fatigue, or in the absence of skill, [for example, in a new kinematic breathing pattern,] a patient tends to innervate muscles that only indirectly help in performing the task, thus reducing efficiency.

The task-specificity in motor skill development is probably influenced by the force-velocity characteristic of the muscle. The amount of force exerted during a particular movement pattern is related to the speed at which the movement is performed. Furthermore, respiratory frequency will tend to fit the rhythm of the cyclical or walking movements of the body[^5] and therefore be repetitious and regular. It is possible that the task learning that took place, for example, on the cycle, would not be transferred to the treadmill because of a different
rhythm or speed of movement. This would explain the task-specific aspect of the changes noted by Paez. Other issues in motor learning can be discussed here. The stimulus to ventilation during the cycle or treadmill exercise is neurogenic, coming initially from the proprioceptors in the limbs. This contrasts with the ventilatory muscle training where the stimulus to increase ventilation is primarily voluntary. Under different conditions, it might be thought more likely that the neurogenic, automatic pathway will be recalled before the voluntary pathway. Conversely, the previous finding would suggest that voluntary control is important in the learning of a new movement, prior to becoming subcortical or automatic. An additional perspective is that the cycle or treadmill exercise resulted in increasing the efficiency of the muscles in the lower limb rather than the ventilatory muscles. Thus, the specific muscles improved may not all be used in a different movement. It is important to realize that the supraspinal level of control is in terms of patterns of movement and not individual muscles. Training of the ventilatory muscles may hold a distinct advantage therefore in that their gross overall co-ordinate pattern of movement will be unchanging, regardless of the task. Thus, it might be said that the 'act of breathing' is being trained, or learned.

Gross and coworkers\(^6\) have observed the effects of task learning when training the diaphragm in quadriplegic patients. They observed that the sternocleidomastoid was used less after training than before, minimal or no EMG activity being recorded. Belman and Fanta both report transfer of the effects of exercise to other instruments.
3.7.3 **Biochemical Adaptation**

There is increasing evidence from animal studies that the limb and ventilatory muscles may adapt to endurance exercise by increasing their oxidative capacity. This occurs by an increasing of the mitochondrial content of the muscle fibres. The evidence appears to be that an increase in oxidative capacity occurs in all three types of muscle fibres rather than a change from fast twitch, slow oxidative, high glycolytic, easy fatiguable fibre (FOG) to a slow twitch, high oxidative, low glycolytic, more difficult to fatigue fibre (SO).

If an increase in muscle aerobic capacity occurs in humans, increased efficiency identified by a reduction in demands of the particular muscle during submaximal workloads would be expected. At rest, the ventilatory muscles in healthy adults require approximately 0.5 to 1.0 ml of oxygen/litre of ventilation. With increasing ventilation, the oxygen cost per unit ventilation becomes progressively greater. It has been estimated that the respiratory muscle during heavy work may tax as much as 10% of the total oxygen uptake. In CAO the oxygen cost is considerably greater. However, the pulmonary ventilation may be a limiting factor even though the maximal capacity of the respiratory muscles are not fully taxed. An increase in pulmonary ventilation beyond a certain point may not be useful or possible since all of the additional oxygen gained may be required for the work of breathing. It is conceivable that the oxygen utilization by the ventilatory muscles is so great that the oxygen supplied to the other tissues is reduced. Training the ventilatory muscles to increase their endurance may result
in a reduction in the oxygen consumption of the respiratory apparatus and a greater amount of oxygen available for the other tissues at a given submaximal workload. Activity endurance may then increase under these conditions. Mertens, Degre, and Paez all reported an increased arteriovenous oxygen difference following a treadmill exercise programme and this is in keeping with Varnauskas' observations following endurance exercise in patients with coronary heart disease. This would reflect an increased ability of the working muscle to extract oxygen from the circulation. It is not clear how this might permit the patient limited by shortness of breath, to increase endurance capacity unless a concomitant reduction in blood flow permits a greater proportion of blood flow, and thus oxygen, to other tissues. This would support the before mentioned postulate.

3.7.4 Breathing Mechanics

Fantas' recent investigation of ventilatory muscle exercise in three CAO patients demonstrated an increase in maximum inspiratory pressure at residual volume as well as a decreased oxygen consumption at a submaximal level of hyperpnea. This would suggest that the ventilatory muscles in CAO patients can be trained for both strength and endurance. An improved performance in the inspiratory muscles might demonstrate a change in the overall pattern of breathing. The inspiratory muscle performance may be variable according to the neural drive, the inspiratory load met, the initial length of the muscle, the magnitude of shortening that occurs, and the velocity of contraction. The neural drive in patients with CAO is invariably normal or increased and the
initial length of the inspiratory muscles may be shorter particularly in the presence of hyperinflation. The initial length of the muscle or the lung volume at which the muscles are worked is obviously very important. It might be that Belman's or Fanta's patients trained at, and learned to operate at, a new lung volume. This could be investigated using a body plethysmograph. The extent of contractile shortening that occurs can be evaluated in terms of the tidal volume and Belman claimed an increased mean tidal volume whereas Pierce reported 'slower deeper breaths'. Velocity of contraction could be measured using the mean inspiratory flow. A reduction in respiratory rate has not been reported other than by Pierce. The optimal breathing frequency during spontaneous breathing is probably closely associated with a minimum average force required, which in turn is closely related to oxygen consumption. An improved pattern of breathing, slower and deeper, may be responsible for effecting better distribution of ventilation or matching of ventilation and perfusion permitting better gas exchange. An increased arterial oxygen tension was reported to be correlated with improved endurance capacity.

3.8 Conclusion

Cycle and treadmill exercise for patients with CAO was first reported in the medical literature more than twenty years ago. However, present statements claiming such therapy to be efficacious or effective are based on less than strongly designed studies. It would be optimistic to believe that the new therapy - ventilatory muscle endurance - will be subjected to the rigours of a randomized control trial before
becoming the new conventional therapy. Furthermore, there remains a possibility that both the old and the new therapies result in the same response. Limb exercise has not been investigated in patients with CAO using both ventilatory muscle endurance and total function as outcomes. These issues result in difficult administrative and clinical management decisions but could be resolved within the confines of a single experimental strategy — a factorial design — permitting both the old and the new, singly and in combination to be investigated. This will be discussed in the following chapter.
CHAPTER IV

Research Objective

The primary objective of this proposed investigation is; to determine whether voluntary hyperventilation and cycle ergometer exercise, singularly or in combination, influence the walking tolerance and physical, social and emotional function of patients with chronic air flow obstruction. Walking tolerance is to be measured using a twelve minute walking test, and a progressive multistage treadmill test. A composite measure of physical, social and emotional function will be obtained using the McMaster Health Index Questionnaire.

The strategy is concerned with efficacy; do any or all of the remedial maneuvers result in more good than harm to patients who fully comply with the treatments?

4.1 Factorial Design

The strategy chosen is a two squared factorial, single-blind, randomized controlled trial. The factorial experiment permitting the effects of different factors to be examined simultaneously. Two factors, cycle ergometer exercise and voluntary hyperventilation are to be represented at two intensity levels - low intensity and high intensity, (levels 0, and 1 respectively). By combining the two levels with the two factors, four treatment groups or cells are formed to be compared (Table 4.1).

The following notation will be used for describing the trea-
### Table 4.1
Experimental Cells

**Voluntary Hyperventilation**

<table>
<thead>
<tr>
<th>Cycle Ergometer Exercise</th>
<th>Placebo [PL] (a_0b_0)</th>
<th>Voluntary Hyperventilation [VH] (a_0b_1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(a_0b_0)</td>
<td>(a_0b_1)</td>
</tr>
<tr>
<td>1</td>
<td>(a_1b_0)</td>
<td>(a_1b_1)</td>
</tr>
</tbody>
</table>
ment combinations:

- $a_0b_0$ placebo
- $a_1b_0$ cycle ergometer exercise
- $a_1b_1$ cycle ergometer exercise plus voluntary hyperventilation
- $a_0b_1$ voluntary hyperventilation.

Abbreviations will be used to represent the maneuvers as follows:

- CE - Cycle Ergometer Exercise
- VH - Voluntary Hyperventilation
- CH - Cycle Ergometer plus Voluntary Hyperventilation
- PL - Placebo Exercise Group.

The factorial design provides a test of the possible interaction as well as a test of each main effect; VH and CE. Each replication of the experiment supplies two estimates for the effect of each of the two factors. If the factors do not interact, the response to CE will be the same regardless of the presence of VH. Similarly, the response of VH will be the same whether in combination with CE or not.

The comparison $(a_1b_1-a_0b_1)$ will estimate the effect of CE when VH is held constant at its high level, and the comparison $(a_1b_0-a_0b_0)$ will estimate the effect of CE in the absence of VH. The mean of these two estimates the main effect of the factor CE (Table 4.2).

i.e. When factors independent;

$$\text{main effect of CE} = \frac{(a_1b_1-a_0b_1) + (a_1b_0-a_0b_0)}{2}$$

similarly,
### Table 4.2

**Main Effect Estimates**

<table>
<thead>
<tr>
<th></th>
<th>Voluntary Hyperventilation VH</th>
<th>Response To VH</th>
<th>Main Effect VH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycle Ergometer CE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_0b_0$</td>
<td>$a_0b_1$</td>
<td>$a_0b_1-a_0b_0$</td>
<td>$\frac{[a_1b_1-a_1b_0]+[a_0b_1-a_0b_0]}{2}$</td>
</tr>
<tr>
<td>$a_1b_0$</td>
<td>$a_1b_1$</td>
<td>$a_1b_1-a_1b_0$</td>
<td></td>
</tr>
<tr>
<td><strong>Response To CE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_1b_0-a_0b_0$</td>
<td>$a_1b_1-a_0b_1$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Main Effect CE</strong></td>
<td>$\frac{[a_1b_0-a_0b_0]+[a_1b_1-a_0b_1]}{2}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
main effect of VH
\[
\frac{(a_0 b_1 - a_0 b_0) + (a_1 b_1 - a_1 b_0)}{2}
\]

It can be seen that every observation is used in the estimate of the effect of each of the factors. This contrasts with a single factor design approach, when an observation only supplies information about the effect of one factor. Therefore, a gain in efficiency is established by the factorial design in that two single factor experiments may require twice the total number of patients to equal the precision obtained by the two squared factorial design.

4.1.1 Two Factor Interaction

The two factors may not be independent or additive in their effects. In other words, the level of intensity (0 or 1) of one factor influences the effect of the other factor. For example, the effect of CE may not be the same at the two levels of VH. This can be examined by the comparison
\[
(a_1 b_1 - a_0 b_1) - (a_1 b_0 - a_0 b_0)
\]

similarly the question whether the level of CE influences the effect of VH can be examined by the comparison;
\[
(a_1 b_1 - a_1 b_0) - (a_0 b_1 - a_0 b_0)
\]

which is identical to the comparison immediately before. Two way interaction can be either antagonistic or synergic, depending upon the direction of the significant difference between main effects of the two factors. [Figures 4.4, 4.5, 4.6]. In other words, it is the joint action
of the factors such that their combined effect is greater or less than the algebraic sum of the individual effects.

The choice of a simple two squared factorial design incorporating a combined treatment group has the advantage that it provides not only a broad picture of the effects of each of the factors separately, but also information concerning their combined effects on clinical outcomes. Evidence of interaction or independence can provide notions as to the operative mechanisms of the factors. It can be postulated, for example, that both VH and CE will improve outcomes by improving the efficiency of the respiratory and cardiovascular systems respectively. However concomitant VH training may have a potentiating effect on the cardiovascular training and outcomes particularly in the patients who have severe limitation of their ventilatory capacity. It is realised that the precision of the test for interaction is less than that for the test for main effects. Thus, if a large response favoring a combination therapy were observed, the recommendation would be for further study comparing the combination therapy with the more efficacious single therapeutic agent.

4.2 Methodologic Standards

To establish efficacy of any treatment it is optimal to compare the treatment against no treatment. However each one of the treatments under test are comprised of elements other than the training regimen. Treatment also includes exposure to a training instrument as well as the care, attention and time of the study personnel. The renowned Hawthorne phenomenon established that it is unrealistic to provide
care and attention to the treatment group, ignore the control group and then attribute any difference that may accrue to the training regimen. Thus a PL regimen will act as a control treatment cell with a patient being exposed to the training instruments as well as receiving equal contact, care and time as those in the three other treatment cells. Regardless of the care exercised in equalizing the conditions among the groups, other than the treatment and the test, the equalization will invariably be to a greater or less extent incomplete because of extraneous sources of variation. Random allocation of the patients to the four treatments helps guarantee against bias that may favour or handicap one or more of the groups. A randomization schedule will be established prior to any experimentation. This is discussed in Section 4.6 Allocation. Additional methodologic standards have been identified and discussed by Sackett^139. These are listed below and are dealt with in detail in relevant subsequent sections.

I. Criteria for inclusion into the study stated clearly to facilitate generalizability of the results.

II. Prognostic stratification. Identification of subgroups that will vary in their risk of achieving the target outcomes.

III. Detailed description of therapeutic maneuvers in order that they may be replicated or compared.

IV. Comorbidity – the presence of relevant comorbid conditions identified in all patients.

V. Compliance with the therapeutic regimens determined. To what extent do patients carry out their treatment?
VI. Cointervention. Equivalency of all tests and procedures among all four groups.

VII. Contamination of the comparison group by exposing the patients to the alternative therapeutic regimen either within the study environment or externally.

VIII. Detailed statement of the criteria for determining the outcomes of interest.

IX. Reporting of mortality from all causes.

X. Blindness. It is difficult to blind a patient to the physical types of maneuver under investigation. Blindness can be imposed on those effecting evaluation of outcomes or indeed allocation of treatment, such, that their convictions about the outcomes of the different treatments may not inadvertently or otherwise influence the measurement.

4.3 Research Hypotheses

The three primary research questions are:

I. Does a regimen of VH have an effect on the study outcomes in patients with chronic airflow obstruction?

II. Does a regimen of CE have an effect on the study outcomes in patients with chronic airflow obstruction?

III. Is there interaction between CE and VH in patients with chronic airflow obstruction?

Several diverse questions are therefore to be examined. In this situation, the F-test that treatments have similar effects may average out individual effects. Using the model for a two-factor completely random-
ized design:

\[ y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + e_{ijk} \]

\( y_{ijk} \) is a typical observation,

\( \mu \) is a constant,

\( \alpha \) represents an effect due to factor A,

\( \beta \) represents an effect due to factor B,

\( \alpha\beta \) represents an effect due to an interaction of factors A and B,

\( e_{ijk} \) represents the experimental error.

\( i = 0,1 \quad A_0 = \text{subtraining or Placebo dosage VH}, \quad A_1 = \text{training VH}. \)

\( j = 0,1 \quad B_0 = \text{subtraining or Placebo dosage CE}, \quad B_1 = \text{training CE}. \)

\( k = N = \text{Number of patients in each cell} \quad = r. \)

At the outset, specific contrasts will be tested by subdividing the overall sum of squares into its component parts.

\[
\sum_{i=1}^{a} \sum_{j=1}^{b} (y_{ij} - \bar{y})^2 = \sum_{i=1}^{a} \sum_{j=1}^{b} (\bar{y}_{ij} - \bar{y})^2 + \sum_{i=1}^{a} \sum_{j=1}^{b} (y_{ij} - \bar{y}_{ij})^2
\]

i.e.

\[ SS_{Total} = SS_{Treatments} + SS_{Residual} \]
The sum of squares for treatments can be further partitioned into 3 parts as follows:

\[
\sum_{i=1}^{a} \sum_{j=1}^{b} (\bar{y}_{ij} - \bar{y})^2
\]

\[
= \sum_{i=1}^{a} \sum_{j=1}^{b} (\bar{y}_i - \bar{y})^2 + \sum_{i=1}^{a} \sum_{j=1}^{b} (\bar{y}_j - \bar{y})^2 + \sum_{i=1}^{a} \sum_{j=1}^{b} (\bar{y}_{ij} - \bar{y}_i + \bar{y}_j - \bar{y})^2
\]

i.e.

\[
SS_{\text{Treatments}} = SS_A + SS_B + SS_{AB}
\]

Since the two factors are at two levels, each of the main effects and the interaction will only have one degree of freedom and will be linear contrasts. The linear contrasts of interest are tabulated in Table 4.3.

The conventional notation is as follows:

A, B denote the main effects of cycle ergometer exercise and voluntary hyperventilation respectively.

AxB denotes interaction.

a, b, \ldots denote one of the two levels at which the corresponding factor occurs. This will be level one. The zero level is signified by absence of the corresponding letter. The treatment combination which consists of the zero level of both factors is denoted by the symbol (1).

Given two linear contrasts of interest, comparisons can be made if all the single degrees of freedom can be incorporated into the same analysis of variance. That is, that the linear contrasts are distributed independent of each other, by demonstrating that the sum of products of the coefficients of the contrasts is equal to zero.
### Table 4.3

Linear Contrasts

<table>
<thead>
<tr>
<th>Contrasts</th>
<th>Effect</th>
<th>TREATMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>$L_1$</td>
<td>A</td>
<td>-1</td>
</tr>
<tr>
<td>$L_2$</td>
<td>B</td>
<td>-1</td>
</tr>
<tr>
<td>$L_3$</td>
<td>A×B</td>
<td>+1</td>
</tr>
</tbody>
</table>
Orthogonal Contrasts (Table 4.4a,b,c).

The functions A, B, A×B satisfy the conditions for an orthogonal set and therefore the squares of the factorial effects divide the treatment sum of squares into three components, each with one degree of freedom.

\[
\text{Treatments } SS_{\text{Total}} = \frac{L_1^2}{4r} + \frac{L_2^2}{4r} + \frac{L_3^2}{4r}
\]

when \( r \) = number of subjects in each treatment and assumed to be equal for each group.

Consider question I:

*Does VH have an effect on stated outcomes ...?*

\[
H_{01}: \mu_{\text{VH}} = \mu_{\text{PL}}
\]

\[
H_{A1}: \mu_{\text{VH}} \neq \mu_{\text{PL}}
\]

Contrast

\[
L_1 = -\frac{T_a}{L_1} + T_a - T_b + T_{ab}
\]

and

Effect A: \( \hat{VH} = \frac{1}{2L_1} \)

Sum of squares for effect A(L₁) in the ANOVA

\[
(SS[L_1]) = \frac{L_1^2}{4r}
\]

Similarly consider question II:

*Does CE have an effect on stated outcomes ...?*
Table 4.4
Orthogonal Contrasts

<table>
<thead>
<tr>
<th>Linear Contrasts</th>
<th>(l)</th>
<th>a</th>
<th>b</th>
<th>ab</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) L₁</td>
<td>-1</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td>L₂</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td>Product</td>
<td>-1</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) L₁</td>
<td>-1</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td>L₂</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td>Product</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) L₁</td>
<td>-1</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td>L₂</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
<td>+1</td>
<td>= 0</td>
</tr>
<tr>
<td>Product</td>
<td>-1</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>= 0</td>
</tr>
</tbody>
</table>
\[ H_{02}: \mu_{CE} = \mu_{PL} \]
\[ H_{A2}: \mu_{CE} \neq \mu_{PL} \]

\[ L_2 = -T(1) - T_a + T_b + T_{ab} \]

Contrast

Effect B: \[ \hat{CE} = \frac{L_2}{2} \]
\[ SS[L_2] = \frac{L_2^2}{4r} \]

Similarly considering question III:

Is there interaction between VH and CE?

\[ H_{03}: \mu_{ab} - \mu_a = \mu_b - \mu(1) \]
\[ H_{A3}: \mu_{ab} - \mu_a \neq \mu_b - \mu(1) \]

Contrast

\[ L_3 = T(1) - T_a - T_b + T_{ab} \]

Effect A \times B: \[ \frac{L_3}{2} \]
\[ SS[L_3] = \frac{L_3^2}{4r} \]

4.4 Population Sources

The study is to be tentatively operational at the Chedoke-McMaster Hospital Rehabilitation Unit. The patient population in 1979 referred to that Unit consisted almost entirely of patients diagnosed as having chronic airflow obstruction. Some 110 patients in 1979 were described as being symptomatically dyspneic on exercise. Cycle ergo-
meter exercise is presently a major element of the present respiratory rehabilitation programme in that Unit. Support for the study will come from both the rehabilitation programme director and the director of the regional respiratory programme. A letter jointly authored by the above directors will be sent to selective general practitioners and the respiratory physicians in the four major regional hospitals: Hamilton General Hospital, Henderson General Hospital, St. Joseph's Hospital and Chedoke-McMaster Hospital. It is anticipated that this letter, inti-
mating the aim of the study and requesting their assistance, will re-
sult in an increased referred population.

4.5 Eligibility Decisions

4.5.1 Diagnostic Criteria

The pathologies of primary concern are pulmonary emphysema and chronic bronchitis. Diagnoses will be obtained using the following criteria:

a. A forced expiratory volume in one second (FEV₁₀) value of less than 60% of that predicted for age and standing height. The predicted values are to be taken from published tables.

b. A ratio of forced expiratory volume in one second to forced vital capacity (FVC) less than 60%.

The measurement procedure will be that recommended in the Epidemiology Standardization Project. Two practise blows will be followed by three measured blows. The largest of the three measurements of FVC and FEV₁₀ are selected even if the two values do not come from
the same curve and the measurements will be documented in a standard form (Appendix I). The apparatus used will be a Vitalograph Dry Spirometer\textsuperscript{44} which will be required to meet the dimensions in the before mentioned project\textsuperscript{51} and further explored in separate studies\textsuperscript{62,158}. The reported one weakness in the Vitalograph has been corrected, in that the chart recorder can now be started prior to the initiation of the expiration.

Two technicians (used interchangeably with the term 'observers') will be trained to obtain the measurements, prior to the study. An estimate of agreement between the two will be formally tested using the analysis of variance (ANOVA) measure of agreement for continuous data: the intraclass correlation coefficient\textsuperscript{14}. The need for two technicians is based on a logistical decision, realizing that relying on one person for all the measurements for a period of one year may be hazardous and could result in missing data. The introduction of a new technician could influence the admission criteria. The agreement study will be carried out on a population of ten patients assigned in random order to each of the observers who will carry out the procedure without the presence nor within the hearing distance of each other. The computation model is described in Section 4.9.1. Variability between the observers will necessarily be no greater than 8%. Periodic checks will be made throughout the study to ensure that technique is unchanging and degree of agreement will be again measured on completion of the study.

A detailed standardized respiratory symptom questionnaire (ATS-DLD)\textsuperscript{32,51} (Appendix III) will be self-administered and will be required
to support the laboratory diagnosis of CAO. This will be given to the patient during the initial clinic visit prior to being examined by the clinic physician. All patients referred to the programme will be examined by the same one physician. To ensure the physician reliability in identifying eligible study patients (see also Sections 4.5.2, 4.5.3, and 4.5.4) a pre-study sample of patient with CAO will be examined by the admitting physician and a member of the investigation personnel separately. A standardized check form (Appendix II) will be used to assist in ensuring that specific issues will be examined for. The result of each pair of examinations will be compared immediately on their completion. Acceptable level of performance will only be achieved after three pairs of examination upon different patients, and will be defined as both the absence of any missing responses on the check form and agreement on the direction of the response.

4.5.2 Severity of CAO

Selection of study patients will be further determined by their severity of CAO as follows:

a. An endpoint of subjective complaint of dyspnea to a standard progressive exercise test will be required for inclusion.

b. The patients who are unlikely to benefit from the described maneuvers are those whose arterial blood oxygen saturation falls below 85% during exercise. Such patients should be tested to see if they can improve their activity tolerance by exercising with supplemental inspired oxygen. During the progressive exercise procedure, the arterial blood
oxygen saturation will be continuously monitored noninvasively using an ear oximeter (Hewlett-Packard 47210A)\textsuperscript{12,143}. All patients demonstrating arterial oxygen saturation less than 85% at any time during the progressive exercise tests will be excluded from admission into the study.

4.5.3 **Age**

Severity of CAO criteria for inclusion will have a narrowing effect on the age spectrum of the experimental population. It is unlikely, if many, or any, patients younger than 30 years of age will meet the inclusion criteria given the natural history of CAO\textsuperscript{116}. No lower age limit will therefore be identified. Patients who will have reached their seventieth (70) birthday prior to entry into the study will not be included. It is deemed likely that the ability of the muscular system to be trained from a neuro-muscular and motivational aspect is less strong than in younger patients.

4.5.4 **Exclusion Criteria**

Comorbid conditions may have major prognostic effects that would produce sources of bias in the post therapy results. However, if comorbid criteria are over employed in excluding patients from the experiment, the resultant population, (if it can be found) may stray more distant from the true state of the chronic airflow obstruction population. The clinic physician will use the standard assessment form.

Exclusion criteria are as follows:

a. Presence of any central nervous system or spinal disorder that may influence operation of the respiratory system, i.e. Those conditions involving: (i) pyramidal system, (ii) extrapyramidal system including the cerebellum, and (iii)
spinal cord.

b. Any neurological, vascular or orthopaedic disorder of the lower limbs that affect the patient's ability to walk or cycle. e.g. Intermittent claudication, symptomatic degenerative arthritis of hip or knee. The primary limiting factor to the activity should be pain.

c. Chronic valvular heart disease.

d. Cardiac rhythm or conduction deficit identified using a 12 lead ECG at rest or during exercise (see Section 4.7.2).

e. Ischaemic heart disease, only if the progressive exercise test is limited by cardiovascular function rather than dyspnea of pulmonary origin. (see Section 4.7.2).

f. Asthma, being defined as follows. Improvement of FEV_{1.0} greater than 30%^{145} as well as an increase of 300 ml measured 20 minutes after inhalation of 200 µg of salbutamol aerosol.

g. Any patient demonstrating any other disease or condition which is likely during the study period to require additional regular medical attention will be excluded or delayed from entering the study.

4.5.5 Stability of CAO

To ensure that no major change in their pulmonary status is occurring at the time of admission into the study and on exposure to the experimental maneuvers, patients will be required to demonstrate no change (≤15%) in either FEV_{1.0} or vital capacity measured on three sep-
arate occasions for a period of four weeks. Pulmonary infection requiring drug therapy, or, any need for hospitalization within the same four week period will result in postponement in entry into the study until an uninterrupted four week period has elapsed without change in FEV$_1.0$ or vital capacity. Similarly, identification of exacerbation during the study period will result in disqualification from the study but not the rehabilitation programme.

4.5.6 Compliant Sample Identification

Entry to the experimental sample will be restricted to those who appear particularly likely to maintain the assigned maneuver and to continue, under investigation for the duration of the study. The absence of non-compliant patients from the initial study sample is not to be considered a serious bias in the report of the analysis of outcomes. The intent is to report on the efficacy of the maneuvers. By identifying the compliance sample prior to the randomization procedure the number of drop outs and incomplete compliant patients will be minimized. Fewer patients will have been exposed to a reduced dosage with a resultant possibility of a reduced training response. Both of which result in the need of a larger sample size to demonstrate real differences between the treatment and control groups.

It would be optimal to predict a patient compliance level for a specific period of time. This was examined in a group of 136 children

*COMPLIANCE: A second but different use of the word 'compliance' relates to a person's behaviour. It is defined as the extent to which a patient follows the exercise protocol in terms of the number of attendances and the pattern of attendance (see also Section 4.7.6)
and adolescents who were on oral penicillin prophylaxis for rheumatic fever. An initial sequence of three weekly urine tests identified 77% of all non-compliers with a non-compliance of 90.2 over a five month period. Three positive urine specimens provided a compliance of 75.6%. Compliance being defined as 75% or more of the tests positive and non-compliance being less than 26% of urine tests positive. This same study also showed that patient non-compliance was associated with broken appointments. By analogy it is suggested that by characterising the patients on the basis of pre-experimental sequence of three weekly test events, it may be possible to define a more compliant experimental sample.

The compliance maneuver which all patients will be exposed to is an educational package designed to teach basic information on CAO using video cassettes as well as discussing issues such as the use of drug therapy, mechanism of breathing, chronic bronchitis and emphysema. Criteria for compliance and therefore admission to the study sample will be attendance at all three sessions. The three weekly visits will occur during the period committed for establishing chronic airflow obstruction stability. Thus, no unnecessary delay will occur between referral to, and commencement of, exercise programme. Strategies directed at improving or maintaining patient compliance will be applied throughout the programme. Following referral to the rehabilitation programme the patient will receive a letter within one week briefly detailing the reason for referral and the possible benefits that may accrue, without mention of a study. An appointment for examination by
the initial examining physician will also be included in the letter. A phone reminder will be made by the receptionist/secretary two or three days prior to the appointment date. No mention of the study will be made until following the compliance measurement. A detailed description of those patients excluded from the study will be maintained and recorded. Compliance during the experimental period is discussed in Section 4.7.7 "Preservation of Protocol".

4.5.7 Ethical Considerations

Those patients who do not meet the inclusion criteria will be offered the usual pulmonary rehabilitation programme, and will not be involved in any part of the study. Similarly, patients who meet the inclusion criteria and who do not wish to enter into the study will be offered the same programme. All patients meeting the inclusion criteria will be informed of the nature of the study, the risk that may be involved, and what will be expected of them. Those wishing to enter into the study will be assured of confidentiality and will be requested to complete a consent form (Appendix IV) permitting them to withdraw at any time from the study without jeopardizing their further care.

If, on the analysis, one maneuver is found to be more efficacious than others, then, given the chronic nature of the pathological condition, it will be possible to offer the maneuver to those who did not receive it.

4.5.8 Summary of Inclusion/Exclusion Criteria

4.5.3.1 Inclusion

1. $\text{FEV}_{1.0}$ less than 60%.
2. FEV_{1.0}/FVC ratio less than 60%.
3. Supporting clinical examination.
4. Dyspneic with exercise test.
5. Four week stability of CAO.
6. Compliant.
7. Willing consent.

4.5.8.2 Exclusion
1. Exercise oxygen saturation less than 85%.
2. Exercise capacity limited by other than CAO.
3. Age greater than 70 years.
4. Asthma.
5. Additional medical attention.

4.5.9 Prestudy Order of Events
4.5.9.1 Initial Visit
   Self-administration of questionnaire.
   Physician assessment.
   Mixed venous \text{\$}$CO_2$.
   Height.
   Weight.
   Lung volume measurements including D_L co.
   Spirometry I.
   Bronchodilator.
   Spirometry II.
   Chest X-ray.
4.5.9.2 Visit Two

Spirometry.
Electrocardiograph.
Progressive Cycle Exercise Test.
Electrocardiograph.
'Rest'.
Four Minute MVV Test.

4.5.9.3 Visit Three

Spirometry.
Electrocardiograph.
Progressive Cycle Exercise Test.
Electrocardiograph.
'Rest'.
Four Minute MVV Test.
Summary of events to patient.
Appointment for education sessions.
Data compiled and given to Admissions Officer.

4.6 Allocation

4.6.1 Prognostic Stratification

Homogeneity may be claimed for the defined initial state of the experimental sample but the patients may still be heterogeneous in various features that determine susceptibility to the target outcomes. Efficiency in comparison can be increased by identifying those patients who are extremely likely (or unlikely) to achieve the target outcomes. Formation of subgroups or strata prior to the random allocation of the
remedial maneuver can result in equal distribution of patients with the
prognostic feature(s) among the four cells. The need for prognostic
strata in this design has been reduced by the choice of admission
criteria for the experimental sample. This has resulted in exclusion
of patients with a very mild CAO, as defined by having little effect on
FEV\textsubscript{1.0} 107 and who are not symptom limited by dyspnea. Patients who
are unlikely to benefit from the described maneuvers are those whose
blood oxygen saturation falls below 85\% during exercise 38,157. They
have also been excluded. Extraneous sources of variation not identifi-
able, may favour one or more of the treatment groups. This effect will
be minimized by pre-experimental randomization. In conclusion it is
deemed that no stratification is required.

4.6.2 Randomization

A randomization schedule for the allocation of patients entered
into the study to one of the four treatment groups will be developed
from a table of random numbers\textsuperscript{53} prior to the study. Each cell will
have the same number of patients at the end of the experimental intake.
The schedule will be maintained by one member of the investigation team,
the admissions officer. The order will not be made known to anyone.
The maneuver allocated by the admissions officer will only be made known
following formal admission of the patient into the study having met all
eligibility criteria including the written consent. The allocation
procedure will necessarily permit the four treatments to be tested
concurrently.
4.6.3 Sample Size Determination

Estimation of the number of patients required to test each of the hypotheses requires knowledge of the following values:

1. Delta (Δ), the magnitude of the difference in pre/post change on each test that can be considered clinically important. This has been derived for the 12 minute walk test (see Section 4.8.3) from the literature and in conversation with clinical practitioners. It is to be equal to 200 m. The Δ for the progressive treadmill test is 30 seconds at the same level of test. A study of chronic respiratory patients using the McMaster Health Index Questionnaire is presently nearing completion and it is hoped to be able to derive a clinically important difference from that data.

2. An estimate of the standard deviation (σ), the amount of variability of all the pre/post changes around the mean pre/post change as expressed by the standard deviation. This has been obtained from the literature and local unpublished measurements.

3. Alpha (level or type one error probability) (α). A probability that such a difference among the treatment groups will occur by chance. i.e. The rate of rejecting a true null hypothesis. This will be set at the conventional level of 0.05.

4. Beta (or type two error) (β). The probability of detecting no difference when one really exist. The compliment of β (1-β) is a power value of the test and it will be equal to 0.8. The closer the power of the test is to 1 the better, however, this also increases the sample size which may have practical and financial limits.
5. The number of cells in the analysis, the experimental design and the degrees of freedom for each factor being analysed.

Cell Number = 4

Factorial 2×2

Degrees of Freedom = 2 - 1 = 1.

6. The required sample size for each of the four cells (n_c). The cells will be equal in number and n_c will be calculated using the previously stated values. The test of various effects will demand different n_c which must be resolved into a single N_total. This will alter the power value of certain effects [increase power value for VH].

7. Loss of patients from initial referred sample due to not meeting the admission criteria, and drop outs during the study.

Voluntary Hyperventilation

α = .05

(1-β) = .80

\[ u = 2 - 1 = 1 \]

f = effect size^{30} which is calculated using the clinically important Δ, and σ, within the populations.

\[ f_{VH} = 0.46 \]

Using formula (8.4.1) for non-tabled f values

\[ n' = \frac{n_{0.05}}{400f^2} + 1 \]

n_{0.05} = tested SS for given α, u and desired power at f = .05

\[ = \frac{1571}{84.64} + 1 \]
\[ n^1 = 19.525 \]

using formula (8.4.4)\(^{29}\)

\[ n_c = \frac{(n-1)(u+1)}{\text{no. of cells}} + 1 \]

\[ n_c = \frac{(19.525-1)(1+1)}{4} + 1 \]

\[ = \frac{37.052}{4} + 1 \]

\[ = 10.263 \]

\[ = 11 \text{ patients per cell} \]

\[ n^1 = \text{above value} = 19.525 \]

\[ u = \text{df for patient VH} = 2 - 1 = 1 \]

\[ f = 4 \]

\[ n_c = 11 \]

\[ \text{VH N} = 44 \]

Similarly for CE

\[ \alpha = .05 \]

\[ (1-\beta) = .8 \]

\[ u = 2 - 1 = 1 \]

\[ f = 37 \]

\[ n^1 = 29.69 \]

\[ n_{CE} = 15.34 = 16 \text{ patients per cell} \]

\[ N_{Total, CE} = 64 \]

A sample size of 64 patients (rather than 44) will thus be required to
test the hypothesis stated. The initial sample required is to be estimated such as to allow for a loss of patients. Using 110 as a projected minimal total of patients referred (based on past referral pattern) the experimental sample size is estimated:

Table 4.5
Summary of Loss From Referred Sample

<table>
<thead>
<tr>
<th></th>
<th>% Loss</th>
<th>No. Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Projected <strong>minimal</strong> referred</td>
<td></td>
<td>110</td>
</tr>
<tr>
<td>Initial loss to exclusion criteria</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Loss to compliance maneuver</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Dropouts during programme</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Loss to illness, etc.</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

This represents 2 patients less than the calculated sample size for the study. It is anticipated that the under-referred pattern common to pulmonary rehabilitation and observed locally can be partly resolved resulting in an increased referred sample magnitude without forgetting about Fineagle's Law.
4.7 Treatments

4.7.1 Introduction

The two factors under investigation are CE and VH each at two levels. Thus four treatment groups will be formed.

The principle variable that influences the response to the endurance exercise training regimen is the intensity of effort relative to the individual patient's maximum or symptom limited functional capacity. A training effect is also influenced by the duration of the exercise session and to a lesser degree by the frequency of the exercise. A known workload which places the same relative load upon each patient at every session of set duration and frequency is thus an optimal regimen to effect an endurance training response.

In chronic airflow obstruction, the limiting factor to exercise or physical working capacity is that of a reduced ventilatory capacity, which is limited by the mechanical constraints of the chest wall and lung, as well as possibly the respiratory muscle performance. The target level to be prescribed for the three training groups will therefore represent a proportion of the patient's highest attained exercise ventilation using two different modes: cycle ergometer and a target ventilation breathing circuit.

4.7.2 Prescription for Cycle Exercise

This will be calculated from the results of a progressive multi-stage exercise test carried out in a temperature controlled (between 19 and 23°C) laboratory using an electrically braked and stabilized cycle ergometer (Siemans-Elema EM350). Calibration of the cycle ergo-

* Siemans-Elema, Solna 1, Postfack S-171 20 Sweden
meter using a physical balance will be carried out every three months, including before, and immediately after, the experimental period. The calibration \(^{39}\) will occur over the full range of work and pedalling frequencies.

The performance of a patient may be underestimated and the exercise prescribed at an unnecessarily low intensity as a result of anxiety and unfamiliarity with the test. To minimize this, a short letter will be sent to the patient explaining the procedure and this will again be reinforced immediately prior to the test. Additionally, two tests will be carried out separated by three to six days. The test with the greatest functional aerobic capacity will be used to calculate prescription.

All the exercise tests will be performed in the same one exercise laboratory supervised by both a physician and a technician experienced in the procedure. Each will have demonstrated by observation to the experimental team the ability to perform the test procedures and identify the variables required. Both persons will be capable of providing cardio-pulmonary resuscitation, and emergency equipment will be kept in the laboratory. Means to contact an emergency cardiac team will be available within the laboratory.

4.7.2.1 Test Procedures

The patient will have been requested not to eat a meal during the two hours prior to the test, they will also be provided with light clothes. With the patient sitting on the cycle the position of the saddle is adjusted in order to allow the leg to be almost fully extended at the bottom of the pedal stroke. The respiratory mouth piece is
<table>
<thead>
<tr>
<th>Table 4.6</th>
</tr>
</thead>
</table>

**Symptomatic complaint of:**
- Severe dyspnea
- Chest pain
- Dizziness
- Faintness

**Observation of:**
- Decreased neuro-coordination
- Mental confusion
- Central cyanosis

**Ear Oximetry:**
- Oxygen desaturation to less than 85%

**ECG evidence of:**
- Ventricular premature beats
- Ventricular paroxysmal tachycardia
- Arterial paroxysmal tachycardia
- Atrial fibrillation
- Second and third degree heart block
- ST segment displacement:
  - Depression of 0.2 mV or greater with horizontal or downward slope
  - Horizontal ST segment elevation of 0.2 mV or greater
  - Symmetrical T-wave inversion of 0.3 mV or greater
adjusted for a comfortable position for the head and neck. The handlebars are positioned so that the patient is slightly leaning forward but not that the weight of the upper trunk is being supported by the hands. Following several minutes of cycling without any added load to become familiar with the equipment, the patient rests on the cycle for 10 minutes to permit a relative resting physiological state. Pedalling is commenced at 60 r.p.m. being maintained with the aid of a metronome and verbal instructions. There is no added load during the first minute and it is then increased by 50 k.p.m. each minute until the patient stops because of symptoms or the staff discontinues the test. This will occur given the presence of any one or more of those stated in Table 4.6.

The following variables are measured in conjunction with the exercise test:

4.7.2.2 Electrocardiograph (ECG)

A 12 lead ECG is performed before the test to exclude recent myocardial ischaemic changes and also to provide a baseline for any problem that may occur. The bipolar lead CM5 with one electrode at V5 and the indifferent on the manubrium sternum is continuously monitored during the test and afterwards to ensure recovery without complications. The measure of cardiac frequency is obtained for each workload of the test, during the last 15 seconds of each minute and after increasing the recorded paper speed. This requires frequent calibration checks of the recorder paper speed, calculating the length of paper for one minute at both speeds \( k_1, k_2 \). The paper length for 5 RR in-
ternals on the cardiac action potential readout is also calculated \(k_3\). Cardiac frequency is then obtained as follows:

\[
F_C = \frac{(5k_1)}{k_3} \text{ Beats Minute}^{-1}
\]

The pen deflection should also be calibrated: \(10 \text{ mm} = 1 \text{ mV}\).

4.7.2.3 Ventilation

During the test the patient continues to breathe in through a dry gas meter separated by bellows from a mouthpiece which is connected by a Lloyd Valve Box. The expired gas is collected in a tissot spirometer by way of a mixing chamber. Sampling of mixed expired \(CO_2\) concentration is obtained distal to the mixing chamber and measured by an infrared \(CO_2\) meter (Statham-Godart Capnograph)*. Expired oxygen concentration is sampled from a tissot spirometer and measured by a paramagnetic oxygen meter. The room temperature, barometric pressure and relative humidity at the time and place of the test are documented. A volume factor which allows calculation of the volume of gas, in the dry gas meter, and entering the tissot spirometer, from the pen deflection is calculated. Calculation of total ventilation, minute volume, tidal volume, breathing frequency, oxygen consumption and carbon dioxide production are calculated from the measurements as described by Jones. \(^9\)

Corrections are made to all measurements of pulmonary ventilation to convert them from ambient temperature (ATPS) to body temperature by multiplying by a factor based on the saturation vapor pressure of water vapor at 37°C and at room temperature. All the derived calculations of

* Statham-Godart, Bilthoven, Holland
carbon dioxide production or oxygen uptake are to be standardized to temperature and pressure, dry (STPD).

The ventilation is recorded during the final 15 seconds of each minute and the value equivalent to 70% of the ventilation performed during the final minute of the test is calculated. The workload fitting that specific level of ventilation will be identified.

In order that it be known that this level of work can be performed safely, the following procedure is carried out following resting for at least 15 minutes. The patient is required to exercise at the calculated workload continuously for 4 minutes with the ECG monitoring continuously. If no adverse cardiac signs or other clinical signs (Table 4.6) as described previously are noted, the calculated workload will be the pretraining baseline for patients in the cycle ergometer exercise group (CE) and the combined exercise group (CR). For explanation of pretraining baselines, see Section 4.7.5 "Exercise Pattern".

4.7.2.4 Recorder

An eight channel pen writing recorder (Mingograf)* will be used to collect the following variables:

1. Time (seconds)
2. ECG
3. Inspired Air Volume from Dry Gas Meter
4. Expired Gas Volume from Tissot Spirometer
5. Carbon dioxide: Deflections for calibrated gases and from mixed expired gas

* Manufactured by Elema-Schönander Ltd., Sweden
6. Oxygen Concentration from Mixed Expired Gas

4.7.2.5 **Blood Pressure**

Systolic blood pressure will be measured and documented at one minute intervals throughout the test by auscultation of the brachial artery using an inflatable cuff and a manometer to register the cuff pressure. A stethoscope diaphragm will be secured by a strap and the trained observer registers the first Korotkoff sound as the systolic blood pressure. Noise may be reduced if the stethoscope tubing hangs vertically downward from the cuff avoiding contact with the upper arm.

4.7.2.6 **Arterial Oxygen Saturation**

This measure will be obtained throughout the exercise test non-invasively using an ear oximeter [Hewlett-Packard 47201A]. The final measurements will be derived from a calibration curve. An oxygen saturation of less than 85% during the exercise test will result in exclusion from the study (Section 4.5.2).

4.7.2.7 **Calibration of Tissot Spirometer and Dry Gas Meter**

(Parkinson-Cowan Limited) CD4

Potentiometer recording of the dry gas meter is to be calibrated against a tissot spirometer. It will additionally be calibrated against a gas syringe which in turn will be calibrated by displacement of a known volume of water. The calibration against the graduated gas syringe will occur at varying volume of gas. The reproducibility of the potentiometer records from the spirometer and gas meter will be checked by measuring the pen deflection with repeated identical volumes of gas.

---

* Hewlett-Packard - Vertek, Palo Alto, CA, U.S.A.
4.7.2.8 Infrared CO₂ Analyzer

Calibrated before and after each test using three different gases each with different concentration of carbon dioxide.

4.7.2.9 Paramagnetic Oxygen Analyzer (Beckman Instrument, Incorporated) (Palo Alto, CA. U.S.A.)

Calibration is similar to that of the CO₂ analyser using calibration gases which should be analysed by a Lloyd Haldane Analyser. Duplicate analysis should agree to within 0.03%. Room air yielding on analysis an oxygen concentration between 20.91 and 20.95%.

4.7.3 Prescription for Voluntary Hyperventilation

The laboratory conditions for this test procedure will remain the same as described for cycle ergometer (4.7.2). The patient will be informed of the procedure and prepared in the same manner as before.

The voluntary hyperventilation maneuver entails requesting a patient to maintain a target level of ventilation, which is maximal for that individual, for four minutes continuously. The principle problem that has to be overcome is that of getting the patient to choose a level of ventilation which he can sustain for four minutes and yet be the maximum [4'MVV]. The second difficulty is that of minimizing hypocapnia during the maneuver. How these are to be overcome follows. The circuit has been previously described²⁶,⁵⁹,⁶⁰. The patient inspires through a dry gas meter and is asked to keep up with a target level of ventilation. The hypocapnia is minimized by a partial rebreathing circuit and the addition of dead space²⁶.

4.7.3.1 4'MVV Circuit

The patient breathes in through a dry gas meter and a low resis-
tance value. [Figure 4.2]. A set of bellows are situated between a dry
gas meter and valve to ensure that the flow to the gas meter is smooth.

If alveolar ventilation is increased without a corresponding in-
crease in CO₂ production, as happens in voluntary ventilation the arter-
ial and venous CO₂ tension falls. This can manifest itself in terms of
reduced cerebral blood flow and dizziness which will terminate or in-
fluence the exercise. Hypocapnia can be prevented by the addition of
CO₂ to the inspired gas but can also be carried out by having a parti-
al re-breathing circuit. The remainder of the inspiratory circuit has
two lines in parallel to each other. One is a tube with a screw-clip
capable of completely occluding the tube and the other consists of a
rubber anesthetic bag within a large glass bottle. The bottle is airtight except for a hole in its base and the gas can only enter or leave
the bag through the hole in its neck connecting it to the circuit.
Therefore, the patient can breathe from either the bottle and bag cir-
cuit or the tube circuit. If the rubber tube is completely occluded by
the screw-clip, the patient re-breathes from the bag and the change in
volume in the bottle ventilates the remaining circuit. By altering the
degree of occlusion, the proportion of the total ventilation which is
re-breathed can be varied, and this with the dead space (600 ml) keeps
the PCO₂ constant. This can be observed using the infra-red CO₂ ana-
lyser.

4.7.3.2 The Target

The target is a pointer mounted above a dry gas meter, and dri-
ven by an electric motor. It can rotate at various speeds in the same
plane and around the same axis as the pointer on the gas meter dial.
Figure 4.2
Voluntary Hyperventilation Circuit

Screwclip

Mouthpiece

Bag-in Bottle [Rebreathing]

Valve

Bellows

Electric Motor

Target Needle

Gas Meter Needle

Gas Meter
The patient is required to breathe hard enough to keep the pointer of the gas meter dial rotating synchronously in phase with the target pointer. The patients will view a mirror reflection of the target pointers closely at eye level. The patient's ability to identify and interpret the movement of the pointers will be checked.

4.7.3.3 Procedure

The patient can choose to be seated on a high stool with feet resting on the ground or to stand. Nose clips are worn throughout the exercise. Initial practice runs will commence at 20 litres per minute and be maintained for four minutes. The patient will be informed that he is to maintain a target level of ventilation for four minutes which is maximum for that period of time. However, he can stop at any time if the effort becomes too uncomfortable.

The target will be set by the experimenter using a stopwatch to time the run and the patient will be encouraged to breathe maximally during the maneuver but not admonished to tolerate distress. If successfully achieved, the target will be progressively increased by 10 litres per minute until it cannot be maintained for four minutes. At least 10 minutes of rest will occur between each attempt. When a level cannot be maintained for four minutes, a further attempt will be made at a level five litres per minute below the failed level. It is unlikely that the speed of the pointer motor will permit finer discrimination than five litres per minute. A small amount of non-alignment between the pointers will be acceptable. Failure to maintain the target level will be defined when the pointers are out of phase by more than 36°.
which is approximately equivalent to 1 litre on the gas meter dial. The highest level of ventilation which can be maintained for four minutes will be termed the four minute maximal voluntary ventilation (4'MVV).

The above measurement will be the pretraining baseline for groups VH and CH.

4.7.3.4 Variables to be Measured and Derived

Ventilation is measured from the gas meter and the volume factor. The product of the latter two is divided by the time (litres minute⁻¹).

Breathing frequency is measured from the record of end-tidal fractional concentration of carbon dioxide.

Tidal volume. This is a derived quotient of ventilation and breathing frequency.

The ECG trace permits monitoring for adverse effects as discussed previously (Table 4.6) and calculation of cardiac frequency.

Arterial blood saturation is monitored continuously by ear oximetry as discussed earlier.

The equipment and recorder is calibrated as before. The circuit will be tested for leaks prior to each test by closing off the expiratory valve and gas meter inlet and blowing hard down the mouthpiece. Absence of the sound of escaping gas on close inspection will indicate an intact circuit.

4.7.3.5 Circuit Resistance

The resistance to the flow of gas through a circuit has been
demonstrated to influence the measurement of 15 second Mw if it is greater than 5 cm H₂O litre⁻¹ second⁻¹ \(^{112,160}\). Resistance to the gas flow less than the above, and no greater than 1.8 cm H₂O litre⁻¹ second⁻¹ on inspiration and less than 1.00 cm H₂O litre⁻¹ second⁻¹ on expiration measured on a circuit very similar to that in this experiment have been reported and will be used as the criteria. The resistance of the circuit will be measured using a procedure similar to that described by Freedman \(^{60}\). "Blowing or sucking air at various flow rates through the apparatus via the mouthpiece and measuring the pressure difference between the mouthpiece and atmosphere".

The pressure difference when air is sucked through circuit represents the inspiratory resistance to the flow of gas measured between the mouthpiece and dry gas meter inlet port. Similarly the expiratory resistance is measured between the mouthpiece and the expiratory valve. The resistance across the circuit is to be measured at four weekly intervals.

**4.7.4 Exercise Treatment Procedures**

The work intensity for all groups will be re-prescribed following a repeat exercise test at four weeks using the same procedures as before. The placebo group will undergo the exercise test but will not increase their work intensity. The work device for cycle exercise (CE) will be a mechanical cycle ergometer braked by a strap (Monark-Crescent AB Varberg, Sweden). Calibration of each of the cycles will occur at four weekly intervals using a known hanging weight in kilograms producing a deflection on the pendulum scale of equal numerical magnitude.
in kg. E.g. A 4kg hanging weight should register 4kp on pendulum scale. Same weights will be used throughout the study. The work device for voluntary hyperventilation (VH) will be the same circuit used in establishing the '4'MV'. To expose the comparison groups to maneuvers that are identical in every way except the "active ingredient", the constituents of the main maneuvers must be considered. Thus, the placebo group will also be exposed to the CE and VH work devices. Like the combined treatment group (CH) the placebo group will be exposed to both work devices and the order will be random. The intensity of the load for the cycle ergometer in the placebo group will be free pedalling at less than 30 r.p.m. without any added load.

The placebo intensity on the VH circuit will be at a target no greater than the resting ventilation of the patient. This will be determined by the ventilation at zero work load during the cycle ergometer exercise test procedure.

An additional constituent that should be considered is the contact time per session. The two single modality groups, CE and VH, will therefore receive a placebo intensity component of equal time and similar patterns prior to the training intensity. (Table 4.7).

4.7.4.1 Exercise Pattern

Fox and Matthews\textsuperscript{58} recommended the following training pattern for improving the aerobic energy systems:

- Training time of 4-5 minutes
- 3 repetitions per set
- Work relief ratio of 1:4.
Table 4.7
Exercise Pattern

<table>
<thead>
<tr>
<th>CE</th>
<th>VH</th>
<th>CH</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4'0</td>
<td>4'0</td>
<td>4'CE₀</td>
<td>4'VH₀</td>
</tr>
<tr>
<td>5'R</td>
<td>5'R</td>
<td>5'R</td>
<td>5'R</td>
</tr>
</tbody>
</table>

Repeated 3 Times

10' - 15' OFF DEVICE

<table>
<thead>
<tr>
<th>CE</th>
<th>VH</th>
<th>CH</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4'1</td>
<td>4'1</td>
<td>4'VH₁</td>
<td>4'CE₀</td>
</tr>
<tr>
<td>5'R</td>
<td>5'R</td>
<td>5'R</td>
<td>5'R</td>
</tr>
</tbody>
</table>

Repeated 3 Times

Order of VH and CE randomly assigned for each of treatment groups CH and PL.

Subscript: 0 = placebo intensity workload

1 = training intensity

R = relief period
Consistent with this prescription an interval work pattern of 4 minute work periods has been chosen. This will enable the patient to perform three runs for each device in a single session without excessive fatigue or boredom. Experience with exercise in respiratory patients indicates that the recovery period should be extended to five minutes following each run. Recovery will be at zero load intensity, but slow free pedalling for several minutes to prevent syncope from peripheral vascular pooling will be permitted. Each session will be split into two parts by a 10-15 minute rest. Total contact time for each session will be approximately 75 minutes.

4.7.4.2 Frequency, Duration and Habituation

The patient will be requested to attend three non-consecutive daily sessions each week for nine weeks. An attendance record will be kept. In an attempt to separate out the habituation effect\(^{40}\), the first three sessions will be termed pretraining. The first exercise session is by necessity required to be at a lower than training intensity, to prevent muscle injuries.

4.7.4.3 Exercise Environment

The external surroundings to the treatment maneuver must be considered. Each of the exercise groups will meet in the same or similar setting at different times. One of the principle roles of the placebo group is to ensure that all the patients are exposed to the therapeutic expectations, personal interaction, care and attention that would not occur if the comparative control was simply no treatment. The frequency and intensity of patients/therapists interchange
in each of the treatment groups is to be equal. This necessitates availability of equal number of personnel for each group.

Patients in placebo group and VH may inadvertently contaminate the experimental protocol by initiating their own cycling exercise at home. Similarly all members of the study population may change their home exercise or activity patterns. An activity log will be requested on three specific occasions during the study period in an attempt to obtain information regarding the source of contamination.

4.7.5 Compliance

Although a compliance sample may have been identified prior to initiating the experimental maneuvers, loss of patients, to illness, having moved away or lack of interest, for example, is still expected. To maintain a potency of work likely to effect a training response, the following criteria for remaining in the study will be used:

A. Absence from programme on greater than 3 consecutive sessions.

B. Absence on greater than 6 occasions in any pattern throughout the study.

Patients thus excluded from the study will continue in the exercise programme.

4.7.6 Preservation of Protocol

A member of the experimental team will be responsible for occasional visiting of each of the training and testing sites to make sure that the protocol is properly carried out. This will help reduce and/or identify contamination, for example, by inadvertent administration of
the high level of exercise to the placebo group. Additionally, co-intervention manifested by unequal attention in the form of additional procedures or vigour of encouragement may be minimized. The latter may be particularly relevant to the placebo group. However, the experimental officer responsible for control over these issues must be separated from testing of the patients in order to maintain the single blind nature of the study.
Figure 4.3

Sequence of Study Events

Baseline Evaluation

Experimental Sample

Random Assignment

Pre-Training Period

Training Period

Post-Training Evaluation
4.8 Target Outcomes

4.8.1 Introduction

The aim of rehabilitation of which exercise programmes constitute a major arm is to enhance the quality of life for the patient. 'Put life into years'.

It is thus indicated that more than physical or physiological measurements are required as target outcomes. Patients with identical degrees of physical limitation may be functioning at greatly different levels of both social and emotional function. Increased walking endurance or exercise tolerance in the laboratory or gymnasium may not be transferred to represent increased function in the home or work environment.

Three outcome measures have been selected:

1. Health Index Questionnaire

"The amount of good that is done varies, and is finally judged in the mind of the patient who is benefitted". - Petty. McMaster Health Index Questionnaire provides a comprehensive perceptual indicator of function: physical, social and emotional health.

2. Twelve Minute Walk Test

An objective endurance measurement which closely resembles everyday function.

3. Progressive Multistage Treadmill Test

An endurance test facilitating physiological variables to be measured.
4.8.2 McMaster Health Index Questionnaire (MHIQ)\textsuperscript{113}

This offers a perceptual indicator of function encompassing physical, social and emotional status. The subjective nature of this questionnaire can be strengthened by the interviewing of a relative or close friend, given the permission of the patient (Question 43, MHIQ). This questionnaire has been tested and continues to be tested in a number of health care environments. In an outpatient rehabilitation setting, the physical function items predicted well the assessments of an occupational therapist and psychiatrist\textsuperscript{57}. The re-test reliability between administration of the question was 0.80. It has also demonstrated sensitivity to change in health and function following release from an acute general medical ward\textsuperscript{22}. Clinical and content validity have been enhanced by weighting of the items by seasoned respiratory rehabilitation personnel\textsuperscript{137}. Questions which include physical function items in terms of activities of daily living probably measure for each patient\textsuperscript{123}:

\begin{itemize}
\item a. physical and functional capacity,
\item b. motivation,
\item c. social dependency,
\item d. a hierarchy of the perceived importance of different activities.
\end{itemize}

It might be expected to find a positive correlation therefore between the tests of endurance and the physical function items, if not the total questionnaire. This could be considered a measure of concurrent validity and could be tested as such. To strengthen the relia-
bility of the weighted items in the questionnaire it would be worthwhile submitting the unweighted questionnaire to an alternative group of health professionals and requesting them to also rank order items. Twenty health professionals including physicians currently working with respiratory patients in a rehabilitation setting would be an ideal group. The degree of relationship between this total rating and that produced by the thirteen respiratory rehabilitation personnel could be determined using a Kendall Rank-Order Correlation (TAU). A "Z" statistic is easily derived from the TAU value and therefore the hypothesis that TAU = 0 can be easily tested.

The final weights will be applied in this study by initially dichotomizing on the basis of face validity all of the MHIQ items to a 0 or 1 response (good or poor function). A score for each question will be calculated, being the product of the response (0 or 1) and the appropriate weight. A pooled index for each patient will then be produced by summing the scores for each question.

\[
\text{Index} = \sum (w_i \cdot r_i)
\]

\[
\begin{align*}
  w_i &= \text{weight for each question} \\
  r_i &= \begin{cases} 
    1 & \text{good} \\
    0 & \text{poor}
  \end{cases} \quad \text{function response}
\end{align*}
\]

The MHIQ as it exists prior to dichotomizing to good or poor function is presented in the Appendices (V) and the weights that will be applied are those to be obtained as a result of surveying the 20 rehabilitation personnel. A team of three respiratory rehabilitation personnel who
are not familiar with the patient or the group they were in, will select cut-off points to collapse the scale to good, fair and poor function. These scales may be further reduced to 'good' and 'not good' function, thus minimizing any central tendency that may have occurred in the reporting.

4.8.3 Twelve Minute Walking Test (12 MD)

A target that is less subjective in that it measures an everyday function activity by actual observation and on a continuous scale of performance rather than on an arbitrary grade of function, may be complimentary to the MHIQ.

A 12MD was originally described by Cooper\textsuperscript{33} when he claimed a close association between the distance covered in twelve minutes running and maximum oxygen uptake measured on a treadmill in healthy men. The reproducibility of the 12MD in patients with Chronic Bronchitis has been demonstrated if performed twice\textsuperscript{110}. However, evidence of reliability does not mean high validity. The 12MD does appear to be clinically credible in that the attribute being measured is walking which might be considered basic to everyday function familiar to all the patients and one that reminds the patient of the limiting nature of their respiratory condition. McGavin also demonstrated that the 12MD positively correlates with a maximum oxygen uptake \( [r = .52; p < .01] \) and ventilation \( [r = .53; p < .01] \) achieved during a progressive cycle exercise test measured concurrently in 29 patients with Chronic Bronchitis\textsuperscript{110}. Belman and Mittman\textsuperscript{11} have reported an increase in the 12 MD following ventilatory muscle training in patients with CAO.
4.8.3.1 Procedure

The patient is accompanied by an experimental officer acting as timekeeper using a stopwatch measuring to 1/100th of a minute. The test is carried out over a meter measured enclosed corridor in a temperature controlled building, free from pedestrian or vehicular traffic. Instructions to the patient are to walk as far as he can in twelve minutes, to choose and adjust his walking pace throughout the test. The patient is to walk continuously if possible but can stop for a rest if necessary. The objective is for the patient to feel that at the end of the test he could not have walked any further. The second test will be performed three days later and the greater of the two measures will be selected. Calibration of the stopwatches will be performed by establishing agreement with a single timeclock measuring to 1/100th of a minute. This will occur both before the study as well as prior to and following the performance of each 12MD.

4.8.3.2 Ancillary Target

Additional to the twelve minute walk test will be calculation of mean stride length, which will be derived from the total number of steps taken in twelve minutes and distance walked.

\[ \text{Mean Stride Length} = \frac{\text{Total Distance Walked in Twelve Minutes}}{\text{Total Number of Steps in Twelve Minutes}} \]

Step number will be obtained from a pedometer worn by each patient during the performance of the test. Calibration of the pedometer will be carried out by a concurrent eyeball count of the number of steps prior to the study.
4.8.3.3 Clinically Important Difference

Based on the medical literature and discussion with clinicians using the twelve minute walk test, a distance of two hundred metres is chosen as the clinical important difference for this study.

4.8.4 Progressive Multistage Treadmill Test

Symptomatic improvement and gains in endurance may be claimed to be psychological rather than physiological responses to exercise training. Although psychological change can be functionally important, the absence of physiological data does not permit further explanation or exploration of the varying mechanisms involved. Cycle exercise may effect improvement in physical function by training of the cardiovascular system. This would be demonstrated, for example, by a reduction in cardiac frequency for a given level of work. This could contrast with the VH group which may demonstrate, aside from improved functional tolerance, a lower oxygen uptake for a comparable submaximal workload, and and increased symptom-limited maximum oxygen uptake, without a reduction in heart rate. These findings could contribute to a claim that the mechanism for training in both groups was different. Cardiovascular system training could have occurred in the CE group while respiratory system training without cardiovascular training having occurred in the VH group. Neither of the two previous stated target outcomes are suitable for optimal measurement of physiological variables. A multistage treadmill test protocol with small increments permits smooth adjustment of the regulatory physiological mechanisms as well as permitting the physiological responses to be evaluated.
at comfortable work levels before proceeding to higher, more stressful
loads. Comparison of responses among patients is easier if more than
one exercise step is employed. This would permit, for example, the
overall breathing pattern to be examined at different power outputs
and at different levels of ventilation.

4.8.4.1 Procedure

To familiarise the patient with treadmill walking, a pretest
walk at a speed not greater than 1.5 m.p.h. for less than two minutes
will be provided. A demonstration by the laboratory personnel will
also be provided. A recovery period will occur between the familiari-
zation procedure and the test run. The patient will be required not to
hold on to the bars during the exercise.

The power output will be increased by a constant amount (1 MET)\textsuperscript{121},
except for the first increment, at the end of each minute (Table 4.8). The test continues to the patients symptom-limited maximum or until
stopped because of adverse signs or symptoms as in Table 4.6. At the
completion of the test the treadmill will be slowed and reduced to 0% grade. Monitoring will continue as previously described.

The variables chosen to be measured at rest and during the
final 15 seconds of each increment are:

- cardiac frequency
- ventilation (litres·minute\(^{-1}\))
- oxygen uptake
- carbon dioxide production
- blood pressure
- respiratory frequency
Table 4.8
Treadmill Test Levels

<table>
<thead>
<tr>
<th>LEVELS</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed mph</td>
<td>0.5</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Treadmill Grade</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.5</td>
<td>2.5</td>
<td>5.0</td>
<td>6.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>
tidal volume

stride length using pedometer.

The highest level of the test, its total duration and the symptom-limited oxygen uptake are also documented. The variables will be examined in relation to each other as indicated by the before mentioned breathing pattern. Similarly, ventilation may be examined at submaximal values of power output or oxygen uptake, as may cardiac frequency.

Measurement of the variables is carried out in the same manner as for the cycle ergometer test previously described (4.7.2). The work rate performed on the treadmill is calculated from the velocity and elevation, plus the patients weight. The treadmill will be calibrated for both speed and angle of elevation prior to the experiment, at three monthly intervals and on completion of the experimental period.

The test-retest reliability of the treadmill outcome and its associated variables will be estimated in the pre-experimental period of the study. The clinically important difference in endurance that will be acceptable is a change of greater or less than 30 seconds of the same level of treadmill test.

4.8.4.2 Ancillary Outcome

Rating of Perceived Exertion

Subjective symptoms provide additional information and are complementary to both the physiological data and the subjective endpoint of an exercise test in that they roughly quantify the intensity of the work. For example, asking the question: how hard is the exer-
exercise? or, how severe is the breathlessness?

This perception of exertion has been studied by Borg who has evolved a scale to quantify measurement of subjective symptoms [Appendix 6]. The perception of exertion may be considered as the subjective cost to the patient which is the overall result of peripheral sensations arising in the muscles and joints as well as central sensations from the respiratory and cardiovascular systems. Borg has claimed a high correlation between heart rate and perceived exertion in patients with the same pathological entity \((r = 0.85)\). The different sensation experienced in different diseases may influence the ratings. Patients with CAO reporting sensation predominantly from breathing difficulties or chest discomfort whereas others may report sensation arising primarily from the legs. Measurement of working capacity calculated from ratings of perceived exertion during cycle or treadmill ergometer work have also been reported and found to be reliable both by correlating two different work levels \((r = 0.91)\) and test-retest reliability at one work level \((r = 0.93)\). Borg reports that physiological variables other than heart rate have been correlated with perceived exertion: oxygen consumption, breathing frequency, body weight and length, blood lactate and blood pressure. Mertens reported absence of change in the rating of perceived exertion at a given workload following the exercise training of patients with CAO. It may be postulated that such a finding minimizes an argument in favor of motivation improving exercise performance. In this study the scale will be used to report intensity of dyspnea immediately on completion of the progressive multistage treadmill test. The procedure will be to show a hardboard
card, with the scale clearly printed on, to the patient and ask the following question: which number on the scale represents your breathlessness during the final seconds of the exercise?

4.8.5 Adverse Effects

All patients denied entry into the study as a result of adverse symptoms during the exercise (Table 4.6) or non-compliance will be described and documented. Similarly, those patients who for whatever reason discontinue the experimental protocol will also be described, including the reason for dropping out. This will include, exacerbations of CAO, muscular injury or other illnesses, and/or mortality.

Desensitisation has been discussed as a possible mechanism resulting in functional gain for the patients; however, it can also be argued that the patients may become more aware of the sensation of dyspnea. Such patients may respond by becoming preoccupied with the symptom or the illness, and 'adopt the sick role'. This could be considered an unwanted side effect of the exercise maneuvers. An analogy may be drawn between this type of response and that reported by Haynes and co-workers investigating absenteeism from work after detection and labelling of hypertension. It was observed that hypertensive patients previously unaware of their illness and its treatment, [were no more likely to take their medicine but] were considerably more likely to demonstrate increased absenteeism than were control hypertensive patients.
4.9 Analysis

4.9.1 Agreement Analyses of Inter-Observer Variation

For introduction to the purpose of this analyses see Section 4.5.1 "Diagnostic Criteria".

In a balanced two-way classification design with three observations per cell, the ANOVA model for random effects of both observers and patients is:

\[ y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha \beta)_{ij} + \epsilon_{ijk} \]

where \( y_{ijk} \) is the kth observation by the jth observer on the ith patient:

- \( \mu \) is the overall mean,
- \( \alpha_i \) is the ith patient effect,
- \( \beta_j \) is the jth observer effect,
- \( (\alpha \beta)_{ij} \) is the interaction between observer and patient.
- \( \epsilon_{ijk} \) is the random error associated with \( y_{ijk} \).

The intraclass correlation coefficient, which estimates the proportion of the total variation attributable to inter-observer variation is:

\[ \hat{p} = \frac{\hat{\sigma}_\beta^2}{\hat{\sigma}_\alpha^2 + \hat{\sigma}_\beta^2 + \hat{\sigma}_{\alpha \beta}^2 + \hat{\sigma}_\epsilon^2} \]

where \( \hat{\sigma}_\alpha^2 \) is the estimate of variance due to observer variation,
\( \hat{\sigma}_\beta^2 \) is the estimate of variance due to patient variation,
\( \hat{\sigma}_{\alpha \beta}^2 \) is the estimate of variance due to observers' rating of the
patient

\( \hat{\sigma}^2 \) is the estimate of variance due to random variation ...

with each of the variance components being estimated as follows:

\[
\begin{align*}
\hat{\sigma}_\alpha^2 &= \frac{[MS_\alpha - MS_{\alpha\beta}]}{m} \\
\hat{\sigma}_\beta^2 &= [MS_\beta - MS_{\alpha\beta}]n \\
\hat{\sigma}_{\alpha\beta}^2 &= [MS_{\alpha\beta} - MS_\varepsilon] \ell \\
\hat{\sigma}_\varepsilon^2 &= MS_\varepsilon
\end{align*}
\]

where \( MS \) = mean square

\( m = j = 2 \) observers

\( \ell = k = 3 \) observations

\( n = i = 10 \) patients.

The data is to be tabulated as in Table 4.9.

The null hypothesis \( \sigma_\beta^2 = 0 \) will be tested using the principle of the comparison of ratios of mean squares to 'F' distributions:

\[
\frac{MS_\beta}{MS_\varepsilon} = F_{1-\alpha,v_1,v_2}
\]

where \( \alpha \) is the probability of falsely rejecting the null hypothesis,

\( v_1 \) is the numerator degrees of freedom,

\( v_2 \) is the denominator degrees of freedom,

when

\[
\frac{MS_\beta}{MS_\varepsilon} = \frac{SS_\beta}{SS_\varepsilon/40} \quad \text{[See Table 4.10].}
\]
Table 4.9
Agreement Analysis: Data Layout

<table>
<thead>
<tr>
<th>Patients</th>
<th>Observers, Replicates</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>Row</td>
</tr>
<tr>
<td>1</td>
<td>$y_{111}$</td>
<td>$y_{121}$</td>
<td>Totals</td>
</tr>
<tr>
<td></td>
<td>$y_{112}$</td>
<td>$y_{122}$</td>
<td>$R_1$</td>
</tr>
<tr>
<td></td>
<td>$y_{113}$</td>
<td>$y_{123}$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$y_{211}$</td>
<td>$y_{221}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$y_{212}$</td>
<td>$y_{222}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$y_{213}$</td>
<td>$y_{223}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>$y_{1011}$</td>
<td>$y_{1021}$</td>
<td>$R_{10}$</td>
</tr>
<tr>
<td></td>
<td>$y_{1012}$</td>
<td>$y_{1022}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$y_{1013}$</td>
<td>$y_{1023}$</td>
<td></td>
</tr>
<tr>
<td>Column</td>
<td>$C_1$</td>
<td>$C_2$</td>
<td>G</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4.10

ANOVA Table for Balanced Two-Way Designs

<table>
<thead>
<tr>
<th></th>
<th>Degrees of Freedom</th>
<th>Sum of Squares ([SS])</th>
<th>Mean Squares ([MS])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>(n - 1 = 9)</td>
<td>(SS_{\alpha} = \frac{1}{6} \sum_{i=1}^{10} R_{i} - \frac{G^2}{60})</td>
<td>(MS_{\alpha} = SS_{\alpha}/9)</td>
</tr>
<tr>
<td><strong>Observers</strong></td>
<td>(m - 1 = 1)</td>
<td>(SS_{\beta} = \frac{1}{30} \sum_{j=1}^{2} C_{j} \frac{G^2}{60})</td>
<td>(MS_{\beta} = SS_{\beta})</td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td>((n-1)(m-1) = 9)</td>
<td>(SS_{\alpha\beta} = \frac{1}{3} \sum_{i=1}^{10} \sum_{j=1}^{2} T_{ij} - SS_{\alpha} - SS_{\beta} + \frac{G^2}{60})</td>
<td>(MS_{\alpha\beta} = SS_{\alpha\beta}/9)</td>
</tr>
<tr>
<td><strong>Error</strong></td>
<td>(nm(\ell-1) = 40)</td>
<td>(SS_{\varepsilon} = TSS - SS_{\alpha} - SS_{\beta} - SS_{\alpha\beta})</td>
<td>(MS_{\varepsilon} = SS_{\varepsilon}/40)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>([nm\ell-1] = 59)</td>
<td>(TSS = \sum_{i=1}^{10} \sum_{j=1}^{2} \sum_{k=1}^{3} y_{ijk} - \frac{G^2}{60})</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.11

Factorial Experiment: Data Layout

<table>
<thead>
<tr>
<th>$\bar{S}$ VH'</th>
<th>$\bar{C}$ VH</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{S}$ CE</td>
<td>$\bar{C}$ CE</td>
</tr>
<tr>
<td>(1)</td>
<td>a</td>
</tr>
<tr>
<td>$s_1$</td>
<td>$s_1$</td>
</tr>
<tr>
<td>$\cdot$</td>
<td>$\cdot$</td>
</tr>
<tr>
<td>$\cdot$</td>
<td>$\cdot$</td>
</tr>
<tr>
<td>$\cdot$</td>
<td>$\cdot$</td>
</tr>
<tr>
<td>$\cdot$</td>
<td>$\cdot$</td>
</tr>
<tr>
<td>$\cdot$</td>
<td>$\cdot$</td>
</tr>
<tr>
<td>$\cdot$</td>
<td>$\cdot$</td>
</tr>
<tr>
<td>$s_{16}$</td>
<td>$s_{16}$</td>
</tr>
<tr>
<td>$c_1$</td>
<td>$c_2$</td>
</tr>
</tbody>
</table>
Table 4.12  
Factorial Experiment: ANOVA Table

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>Degrees of Freedom</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
<th>'F' Ratio</th>
<th>'p'</th>
</tr>
</thead>
<tbody>
<tr>
<td>VH [A]</td>
<td>1</td>
<td>( \frac{[\text{Factorial Effects}]^2}{4r} )</td>
<td>( SS_A/1 )</td>
<td>( MS_A/MS_{\text{error}} )</td>
<td></td>
</tr>
<tr>
<td>CE [B]</td>
<td>1</td>
<td>( SS_B/1 )</td>
<td>( MS_B/MS_{\text{error}} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction [A×B]</td>
<td>1</td>
<td>( SS_{AB}/1 )</td>
<td>( MS_{A×B}/MS_{\text{error}} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td>60</td>
<td>( SS_{Total}-[SS_A+SS_B+SS_{AB}] )</td>
<td>( SS_{\text{error}}/60 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.9.2 Analysis of Variance [Factorial Experiments]

The three primary outcomes discussed in the previous chapter [4.8] will be tested for differences among their means. The statistical procedure used will be the analysis of variance as applied to Factorial experiments.\textsuperscript{145}

The data for each of the outcomes will be collected and tabulated separately as in Table 4.11.

The computation will be based on the model described in chapter 4.1.

4.9.2.1 Computation

The factorial effects totals for $VH[A]$, $CE[B]$ and interaction $[A \times B]$ are calculated from the treatment totals using the multipliers which are the linear coefficients [Table 4.12], e.g. Factorial effect total for $VH$ equals

$$- [1][C_1] + [1][C_2] - (1)(C_3) + (1)(C_4) .$$

Table 4.13

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>a</th>
<th>b</th>
<th>ab</th>
<th>Factorial Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>C_1</td>
<td>C_2</td>
<td>C_3</td>
<td>C_4</td>
<td>Totals</td>
</tr>
<tr>
<td>$VH[A]$</td>
<td>-1</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>$CE[B]$</td>
<td>-1</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Interaction $[A \times B]$</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
<td>+1</td>
<td></td>
</tr>
</tbody>
</table>
The contribution of each factorial effect to the treatment sum of squares is derived by dividing the square of each of the factorial effects total by \( 64(4r) \) [Table 4.12]. The factorial effects means can also be calculated directly by dividing the effect totals by \( 2r \) [Table 4.14]. The effect means demonstrate the direction and magnitude of each of the effects. The remaining calculations to derive the 'F' ratio are summarised in Table 4.12.

<table>
<thead>
<tr>
<th>Factorial Effect Totals</th>
<th>Divisor 2r</th>
<th>Standard Error of the Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>32</td>
<td>( \frac{\sqrt{S^2}}{r} )</td>
</tr>
<tr>
<td>B</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>A\times B</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

The 'p' value corresponding to the 'F' ratio is obtained from published tables.

In the presence of a statistically significant 'F' ratio for the combined treatment group [A\times B] then the nature of a possible interaction can be uncovered by the direction of the significant difference, supported by the clinical and physiological variables. [Figures 4.4, 5, 6].

It is possible that all the patients may, for some unforeseen reason, not be able to effect as great a change in outcomes as others,
Figure 4.4

\[ \Delta \]

Lines Parallel. Main Effects-Independent No interaction

\[ \Delta \]

Figure 4.5

Diverging Lines Synergic interaction

\[ \Delta \]

Figure 4.6

Antagonistic interaction

\[ \bar{\Delta} \text{ is the mean difference for each treatment group} \]
given that they are exposed to an equal potency of work. The shape of the curve for the population of patients may then not be 'normal'. This may be resolved by effecting a transformation of the data. The transformation chosen will be dependent upon the shape of the curve produced but it is realised that the choice of log transformation may present a problem in the presence of an interaction effect. If the two main effects are not independent, log transformation may edit the data to additive thus removing the interaction.

4.9.3 **Missing Data**

Though an intensive effort will be made to minimize the possibility of a missing observation, it is possible that a patient may be unable to participate in an outcome measurement. A decision will have to be made at the time of analysis on which procedure to use. An analysis may be carried out in the presence of a few absent values, or a more complex procedure may be chosen. A preferable method is to derive an estimate for the missing value using an analysis of covariance.

4.9.4 **Multiple Comparisons**

A number of ancillary targets have been stated as well as physiological variables. However, it is recognised that to challenge or dredge the data frequently can result in spurious associations. For example, to maintain an $\alpha$ significance OR further analysis computed thereafter, say 4, requires the analysis to be performed at a significance level of $[(\cdot05\cdot)/4].0125$ or the probability of rejecting one or more of the four hypothesis is less than $0.185 \cdot [a<1-0.95^4]$. A number of procedures have been devised that permit post hoc inspection of differences
between means that may appear large. Newman-Keuls procedure has the property that, the probability of finding a significant difference between any of the treatment means is no greater than the overall \( \alpha \).

However, this multiple comparison method for the other than primary outcomes provides only exploratory analysis of the data and thus may provide support for the primary outcomes but not be outcomes on their own.

This is of particular relevance to the physiological variables measured during the progressive treadmill test. Postulates relating to mechanisms effecting change (or its absence) in overall function may be evolved. [See Section 4.8.4].

It may also be that patients demonstrating different degrees of moderate to severe airways obstruction, gas diffusion capacity or other pulmonary function variable unforeseen in the initial design, demonstrate different magnitudes of change in outcomes. Although the pre-experimental randomisation procedure is likely to handle such confounders exploratory analysis will be carried out between or among means using the analysis of covariance.

4.10 Budget

The estimated duration of the study is 16 months. The initial three months will be for communication with physicians, hiring and training personnel, and testing equipment. The successive ten months will be an experimental period including patient intake and establishing eligibility. The last patient intake should be no later than 8 months into the experimental period. The final three months will be for data computation and the writing of reports. The former will include the
writing of a computer programme.

The major personnel problem may be that of finding exercise leaders. Two persons are needed to be available for each of the groups and it is anticipated that physiotherapy and physical education students will be available. Much of the equipment cost relates to maintenance of equipment although some items will need to be bought.

The total estimated cost of the proposed study is $36,677.16.


### Table 4.15

Outline of Budget

<table>
<thead>
<tr>
<th>Equipment</th>
<th>$</th>
<th>$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ear Oximeter:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance of fiberoptic component</td>
<td>200.00</td>
<td></td>
</tr>
<tr>
<td><strong>Vitalograph:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouthpieces and recording paper</td>
<td>190.00</td>
<td></td>
</tr>
<tr>
<td><strong>Cycle Ergometer:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calibration, tubing, etc.</td>
<td>700.00</td>
<td></td>
</tr>
<tr>
<td><strong>Dry Gas Meter:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 @ $850.00</td>
<td>1700.00</td>
<td></td>
</tr>
<tr>
<td>Capnograph*</td>
<td>150.00</td>
<td></td>
</tr>
<tr>
<td>Oxygen Analyser</td>
<td>250.00</td>
<td></td>
</tr>
<tr>
<td>Low Resistance Valve (Lloyd)</td>
<td>450.00</td>
<td></td>
</tr>
<tr>
<td>Treadmill: Slow speed adaptation</td>
<td>600.00</td>
<td></td>
</tr>
<tr>
<td>Monark Exercise Cycles:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 @ $750.00</td>
<td>2250.00</td>
<td></td>
</tr>
<tr>
<td><strong>VH Target Materials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gases</td>
<td>350.00</td>
<td></td>
</tr>
<tr>
<td><strong>Recorder:</strong></td>
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<td></td>
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<tr>
<td>Galvanometer</td>
<td>475.00</td>
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</tr>
<tr>
<td><strong>Writing Materials</strong></td>
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<tr>
<td><strong>ECG Materials</strong></td>
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<tr>
<td><strong>Pedometers:</strong></td>
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</tr>
<tr>
<td>4 @ $25.00</td>
<td>100.00</td>
<td></td>
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<tr>
<td><strong>Stopwatch:</strong></td>
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<td></td>
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<tr>
<td>3 @ $12.00</td>
<td>36.00</td>
<td></td>
</tr>
<tr>
<td><strong>Education Package</strong></td>
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<td></td>
</tr>
<tr>
<td>Slide Viewer</td>
<td>400.00</td>
<td></td>
</tr>
<tr>
<td><strong>Sub-Total:</strong></td>
<td>8446.00</td>
<td>8446.00</td>
</tr>
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### Supplies

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Questionnaires:</strong></td>
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<td></td>
</tr>
<tr>
<td>ATS-DLD</td>
<td>400.00</td>
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</tr>
<tr>
<td>MHIQ</td>
<td>280.00</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Supplies:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleenex, Paper, etc.</td>
<td>200.00</td>
<td></td>
</tr>
<tr>
<td><strong>Stationary, Stamps, Photocopying</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drugs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutomol Aerosols (12 @ $8.43 each)</td>
<td>101.16</td>
<td></td>
</tr>
<tr>
<td><strong>Sub-Total:</strong></td>
<td>1331.16</td>
<td>1331.16</td>
</tr>
</tbody>
</table>
Table 4.15
Outline of Budget
(continued)

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Computation</strong></td>
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<td></td>
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<tr>
<td>Computer Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keypunching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical Consulting:</td>
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<tr>
<td>20 hours @ $30.00/hour</td>
<td>850.00</td>
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<td><strong>Sub-Total:</strong></td>
<td></td>
<td>600.00</td>
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<tr>
<td></td>
<td><strong>1450.00</strong></td>
<td>+ $1450.00</td>
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<tr>
<td><strong>Salaries</strong></td>
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<tr>
<td>Exercise Leaders: 8</td>
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<tr>
<td>7.50/hour</td>
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<td></td>
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<tr>
<td>4.5 hours/week</td>
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<td>4050.00</td>
</tr>
<tr>
<td>10 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Co-ordinator:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulltime - 16 months</td>
<td></td>
<td>21500.00</td>
</tr>
<tr>
<td>($16,000/annum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sub-Total:</strong></td>
<td></td>
<td>$25550.00</td>
</tr>
<tr>
<td></td>
<td><strong>36677.16</strong></td>
<td></td>
</tr>
<tr>
<td><strong>GRAND TOTAL:</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX I

FEV₁₀ and FVC Report Form
### Laboratory Investigations 'A' Ventilatory Capacity

<table>
<thead>
<tr>
<th><strong>Code No.:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name:</strong></td>
</tr>
<tr>
<td><strong>Address:</strong></td>
</tr>
<tr>
<td><strong>Telephone No.:</strong></td>
</tr>
<tr>
<td><strong>Date of Birth:</strong></td>
</tr>
<tr>
<td><strong>Date of Examination:</strong></td>
</tr>
</tbody>
</table>

| **Standing Height (cm):** | | **Weight (kg):** |
|---------------------------|--------------|

<table>
<thead>
<tr>
<th><strong>Ambient temperature (°C):</strong></th>
</tr>
</thead>
</table>

**One-second Forced Expiratory Volume**
[corrected to BTPS]

<table>
<thead>
<tr>
<th><strong>Observer:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Instrument number:</strong></td>
</tr>
<tr>
<td><strong>Time of day (24 hour):</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Reading 1:</strong></th>
<th><strong>2:</strong></th>
<th><strong>Predicted Value:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3:</strong></td>
<td><strong>4:</strong></td>
<td><strong>5:</strong></td>
</tr>
</tbody>
</table>

Largest of 3, 4, 5
(to two decimal places) [ ] [ ]

**Vital Capacity - Forced**
[corrected to BTPS]

<table>
<thead>
<tr>
<th><strong>Observer:</strong></th>
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<tr>
<td><strong>Instrument number:</strong></td>
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<td><strong>Time of day (24 hour):</strong></td>
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<th><strong>2:</strong></th>
<th><strong>_predicted Value:</strong></th>
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<tr>
<td><strong>3:</strong></td>
<td><strong>4:</strong></td>
<td><strong>5:</strong></td>
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Largest of 3, 4, 5
(to two decimal places) [ ] [ ]

FEV % VC [ ] [ ]
APPENDIX II

Clinical Examination Form
Clinical Assessment

<table>
<thead>
<tr>
<th>Name:</th>
<th>Code No.:</th>
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<tbody>
<tr>
<td>Address:</td>
<td>Code No.:</td>
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<tr>
<td>Telephone No.:</td>
<td></td>
</tr>
<tr>
<td>Date of Birth:</td>
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<td>Date of Examination:</td>
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<table>
<thead>
<tr>
<th>All current medication(s):</th>
<th>DRUG</th>
<th>DOSAGE</th>
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<table>
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<tr>
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<tr>
<td></td>
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<table>
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<th>Heart Sounds:</th>
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<td></td>
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<td>Other (State):</td>
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<table>
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<tr>
<th>(Sitting)</th>
<th>YES</th>
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<th>COMMENTS</th>
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<td>Sternomastoid Contracting at 'Rest'</td>
<td>Yes</td>
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<tr>
<td>Bucket handle movement present</td>
<td>No</td>
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<tr>
<td>Inward inspiratory movement of upper abdomen</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Wheezing on auscultation</td>
<td>Yes</td>
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</table>

| History of chest pain | Yes | |
| History of ischaemic heart disease | No | |
| History of chronic valvular H.D. | | |
| History of leg pain on walking | No | |

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<tr>
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<tr>
<td>Ataxic</td>
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<td>Antalgic</td>
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(continued)
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<td>'Arthritis':</td>
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<td>Hypoactive</td>
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<td>Normal</td>
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<td>Muscles:</td>
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<td>Flaccid</td>
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<td>Atrophy</td>
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<td>Scanning, Speech</td>
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<tr>
<td>Intention Tremor</td>
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<tr>
<td>Dysmetria</td>
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<tr>
<td>Psychiatric Therapy in past 12 months</td>
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<tr>
<td>Other symptoms and/or signs of disease likely to affect exercise training or oxygen transport</td>
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APPENDIX III

ATS-DLD Respiratory Symptom Questionnaire
Respiratory Symptom Questionnaire

Code Number:

Name: ____________________________

Address: __________________________

__ ____________________________

Telephone Number: ________________

Date: ____________________________

1. Date of Birth: Month Day Year

2. Place of Birth: __________________________

3. Sex: 1. Male __________ 2. Female __________

4. What is your marital status? 1. Single ________
2. Married ________
3. Windowed ________
4. Separated/Divorced ________

5. Race: 1. White ________
2. Black ________
3. Oriental ________
4. Other ________

6. What is the highest grade completed in school? 
(For example: 12 years is completion of high school)

continued...
These questions pertain mainly to your chest. Please answer yes or no if possible. If a question does not appear to be applicable to you, check the does not apply space. If you are in doubt whether your answer is yes or no, record no.

COUGH

7A. Do you usually have a cough? (Count a cough with first smoke or on first going out-of-doors. Exclude clearing of throat.) [If no, skip to Question 7C.]
   1. Yes _____ 2. No _____

B. Do you usually cough as much as 4 to 6 times a day, 4 or more days out of the week?
   1. Yes _____ 2. No _____

C. Do you usually cough at all on getting up, or first thing in the morning?
   1. Yes _____ 2. No _____

D. Do you usually cough at all during the rest of the day or at night?
   1. Yes _____ 2. No _____

IF YES TO ANY OF THE ABOVE (7A,B,C, or D), ANSWER THE FOLLOWING: IF NO TO ALL, CHECK DOES NOT APPLY AND SKIP TO NEXT PAGE.

E. Do you usually cough like this on most days for 3 consecutive months or more during the year?
   1. Yes _____ 2. No _____ 8. Does not apply _____

F. For how many years have you had this cough?
   Number of years
   88. Does not apply _____

7G. During which months does your cough give you the most trouble.
   (Check months troubled) OR: Check here if no relation to time of year

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
PHLEGM

8A. Do you usually bring up phlegm from your chest?  
   (Count phlegm with the first smoke or on first going out-of-doors. Exclude phlegm from the nose. Count swallowed phlegm.) [If no, skip to 8C.]  
   1. Yes____ 2. No____

B. Do you usually bring up phlegm like this as much as twice a day, 4 or more days out the week?  
   1. Yes____ 2. No____

C. Do you usually bring up phlegm at all on getting up, or first thing in the morning?  
   1. Yes____ 2. No____

D. Do you usually bring up phlegm at all during the rest of the day or at night?  
   1. Yes____ 2. No____

IF YES TO ANY OF THE ABOVE (8A, B, C, or D), ANSWER THE FOLLOWING: IF NO TO ALL, CHECK DOES NOT APPLY AND SKIP TO THE NEXT PAGE.

E. Do you bring up phlegm like this on most days for 3 consecutive months or more during the year?  
   1. Yes____ 2. No____

F. For how many years have you had trouble with phlegm?  
   Number of years____
   88. Does not apply____

8G. During which months does your phlegm give you the most trouble? (Check months troubled) OR: Check here if no relation to time of year.  
   88. Does not apply____

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
EPISODES OF COUGH AND PHLEGM

9A. Have you had periods or episodes of (increased) cough and phlegm lasting for 3 weeks or more each year? *(For persons who usually have cough and phlegm)*

1. Yes  2. No

IF YES TO 9A:

B. For how long have you had at least 1 such episode per year?

Number of years

88. Does not apply

WHEEZING

10A. Does your chest ever sound wheezy or whistling:

1. When you have a cold?
2. Occasionally apart from cold?
3. Most days or nights?

1. Yes  2. No

IF YES TO 1, 2 or 3 IN 10A:

B. For how many years has this been present?

Number of years

88. Does not apply

11A. Have you ever had an attack of wheezing that has made you feel short of breath?

1. Yes  2. No

IF YES TO 11A:

B. How old were you when you had your first such attack?

Age in years

88. Does not apply

C. Have you had 2 or more such episodes?

8. Does not apply

D. Have you ever required medicine or treatment for the(se) attack(s)?

8. Does not apply
11E. During which months does your wheezing give you the most trouble? (Check months troubled) OR: Check here if no relation to time of year

1 2 3 4 5 6 7 8 9 10 11 12
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec

8. Does not apply

CHEST COLD AND CHEST ILLNESSES

12A. If you get a cold, does it usually go to your chest? (Usually means more than 1/2 the time.)

1. Yes 2. No

8. Does not apply

13A. During the past 3 years, have you had any chest illnesses that have kept you off work, indoors at home, or in bed?

1. Yes 2. No

IF YES TO 13A:

B. Did you produce phlegm with any of these chest illnesses?

1. Yes 2. No

8. Does not apply

C. In the last 3 years, how many such illnesses with (increased) phlegm, did you have which lasted a week or more?

1. Number of illnesses 2. No such illnesses

8. Does not apply

PAST ILLNESSES

14. Did you have any lung trouble before the age of 16?

1. Yes 2. No

15. Have you ever had any of the following?

1A. Attacks of bronchitis?

1. Yes 2. No

IF YES TO 1A:

B. Was it confirmed by a doctor?

1. Yes 2. No

8. Does not apply

C. At what age was your first attack?

_ _ _ _ Age in years

8. Does not apply

16A. Have you ever had chronic bronchitis?

1. Yes 2. No

IF YES TO 16A:

B. Do you still have it?

1. Yes 2. No

8. Does not apply
16C. Was it confirmed by a doctor?

D. At what age did it start?

17A. Have you ever had emphysema?

IF YES TO 17A:

B. Do you still have it?

C. Was it confirmed by a doctor?

D. At what age did it start?

18A. Have you ever had asthma?

IF YES TO 18A:

B. Do you still have it?

C. Was it confirmed by a doctor?

D. At what age did it start?

E. If you no longer have it, at what age did it stop?

19. Have you ever had:

A. Any other chest illness?
   If yes, please specify

B. Any chest operation?
   If yes, please specify

C. Any chest injuries?
   If yes, please specify

20A. Has a doctor ever told you that you had heart trouble?

IF YES TO 20A:

B. Have you ever had treatment for heart trouble in the past 10 years?
21A. Has a doctor ever told you that you had high blood pressure?
   1. Yes  2. No

IF YES TO 21A:

B. Have you had any treatment for high blood pressure (hypertension) in the past 10 years?
   1. Yes  2. No  8. Does not apply

OCCUPATIONAL HISTORY.

22A. Have you ever worked full time (30 hours per week or more) for 6 months or more?
   1. Yes  2. No

IF YES TO 22A:

B. Have you ever worked for a year or more in any dusty job?
   1. Yes  2. No  8. Does not apply
   Specify job/industry Total years worked

C. Have you ever been exposed to gas or chemical fumes in your work?
   1. Yes  2. No
   Specify job/industry Total years worked

D. What has been your usual occupation or job - the one you have worked at the longest?
   1. Job-occupation: ____________________________
   2. Number of years employed in this occupation: ____________________________
   3. Position-job title: ____________________________
   4. Business, field, or industry: ____________________________

22E. What is your most recent job?
   1. Job-occupation: ____________________________
   2. Position-job title: ____________________________
   3. Business, field, or industry: ____________________________
   4. Are you still employed at this job: No
      Yes, full time
      Yes, part time

5. If not working at this job, at what age did you last work at it? ____________________________
TOBACCO SMOKING

23A. Have you ever smoked cigarettes? (No means less than 20 packs of cigarettes or 12 oz. of tobacco in a lifetime or less than 1 cigarette a day for 1 year)

1. Yes  2. No

IF YES TO 23A:

B. Do you now smoke cigarettes (as of 1 month ago)?

1. Yes  2. No

8. Does not apply

C. How old were you when you first started regular cigarette smoking?

1. Yes  2. No

88. Does not apply

D. If you have stopped smoking cigarettes completely, how old were you when you stopped?

1. Yes  2. No

88. Does not apply

E. How many cigarettes do you smoke per day now?

Cigarettes per day

88. Does not apply

F. On the average of the entire time you smoked, how many cigarettes did you smoke per day?

Cigarettes per day

88. Does not apply

G. Do or did you inhale the cigarette smoke?

1. Does not apply

2. Not at all

3. Slightly

4. Moderately

5. Deeply

FAMILY HISTORY

24. Were either of your natural parents ever told by a doctor that they had a chronic lung condition such as:

FATHER  MOTHER

1. Yes  2. No  3. Don't Know  1. Yes  2. No  3. Don't Know

A. Chronic bronchitis?

B. Emphysema?

C. Asthma?

D. Lung cancer?

E. Other chest conditions?
25A. Is parent currently alive

B. Please Specify

<table>
<thead>
<tr>
<th>Age if living</th>
<th>Age if living</th>
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<tbody>
<tr>
<td>Age at death</td>
<td>Age at death</td>
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<tr>
<td>8. Don't know</td>
<td>8. Don't know</td>
</tr>
</tbody>
</table>

C. Please specify cause of death:


APPENDIX IV

Consent Form
Consent Form

Endurance Exercise for CAO

I, .................................................................., freely and voluntarily consent to participate in a research programme under the direction of ........................................ to be conducted in the Chedoke-McMaster Rehabilitation Unit.

I understand that I will receive one of four exercise regimens which will be assigned randomly (like tossing a coin). A thorough description of the regimens has been explained to me, to my satisfaction. If I do not receive the exercise that is proven to be the best after the study is completed, it will be offered to me.

I understand that I may withdraw my consent and discontinue participation in this study without compromising any opportunity for medical care.

I authorize ....................................................... and the Rehabilitation Unit to keep, preserve, use and dispose of the study findings without my name being associated with any of the results.

I have read and understand the contents of this form and have received a copy.

................................................................. Witness

................................................................. Participant

................................................................. Date

I have explained and defined in detail the research procedures to which the patient has consented to participate.

................................................................. Signature

................................................................. Date
APPENDIX V

McMaster Health Index Questionnaire
Self-Administered Form
McMASTER HEALTH INDEX QUESTIONNAIRE
SELF-ADMINISTERED FORM

Directions: Please answer each question by circling the appropriate number. Because we want your answers and opinions, we urge you not to talk about your answers or show your completed questionnaire to anyone.
SECTION A: The questions in the first section ask about your health and whether you are able to do certain things.

1. Today, are you physically able to run a short distance, say 300 feet, if you are in a hurry? (This is about the length of a football field or soccer pitch.)
   1 NO
   2 YES

2. Today, do you (or would you) have any physical difficulty at all with:
   a. walking, as far as a mile?
      1—NO DIFFICULTY
      2 DIFFICULTY
   d. climbing up 2 flights of stairs?
      1 NO DIFFICULTY
      2 DIFFICULTY
   c. standing up from, and/or sitting down in a chair?
      1 NO DIFFICULTY
      2 DIFFICULTY
   d. feeding yourself?
      1 NO DIFFICULTY
      2 DIFFICULTY
   e. undressing?
      1 NO DIFFICULTY
      2 DIFFICULTY
   f. washing (face and hands), shaving (men) and/or combing hair?
      1 NO DIFFICULTY
      2 DIFFICULTY
   g. shopping?
      1 NO DIFFICULTY
      2 DIFFICULTY
   h. cooking?
      1 NO DIFFICULTY
      2 DIFFICULTY
   i. dusting and/or light housework?
      1 NO DIFFICULTY
      2 DIFFICULTY
   j. cleaning floors?
      1 NO DIFFICULTY
      2 DIFFICULTY
3. Today, are you physically able to take part in any sports (hockey, swimming, bowling, golf, and so forth) or exercise regularly?
   1. NO
   2. YES

4. At present, are you physically able to walk out of doors by yourself when the weather is good?
   1. NO
   2. YES

4a. What is the farthest you can walk?
   1. ONE MILE OR MORE
   2. LESS THAN ONE MILE, MORE THAN 30 FEET (THIS IS ABOUT THE SIDE OF A HOUSE)
   3. LESS THAN 30 FEET
   4. BETWEEN ROOMS
   5. WITHIN A ROOM
   6. CAN'T WALK AT ALL

5. Today, do you (or would you) have any physical difficulty at all travelling by bus whenever necessary? (Circle your answer)
   1. NO
   2. YES

6. Today, do you have any physical difficulty at all travelling by car whenever necessary?
   1. NO
   2. YES

7. Today do you have any physical difficulty driving a car?
   1. NO
   2. YES
   3. DO NOT HAVE A DRIVER'S LICENCE

8. Do you wear glasses?
   1. NO
   2. YES

8a. Do you wear glasses for distance or reading?
   1. DISTANCE
   2. READING
   3. BOTH FOR DISTANCE AND READING
   4. DO NOT WEAR GLASSES

8b. Do you have any trouble reading ordinary newsprint?
   1. NO
   2. YES
4c. Do you have a headache after watching television or reading?

1. NO
2. YES

9. Do you wear a hearing aid?

1. NO
2. YES

9a. Do you have trouble hearing in a normal conversation with several other persons?

1. NO
2. YES

9b. Do you have trouble hearing the radio or television?

1. NO
2. YES

SECTION B: Often peoples' health affects the way they feel about life. For these next questions, please circle the choice that is closest to the way you feel about each statement.

STRONGLY AGREE   STRONGLY DISAGREE

10. I sometimes feel that my life is not very useful.

11. Everyone should have someone in his life whose happiness means as much to him as his own.

12. I am a useful person to have around.

13. I am inclined to feel that I'm a failure.

14. Many people are unhappy because they do not know what they want out of life.

15. In a society where almost everyone is out for himself, people soon come to distrust each other.
16. I am a quick thinker.                      1 2 3 4 5  EF
17. Some people feel that they run           1 2 3 4 5  EF
their lives pretty much the way they want to and this is the case with me.
18. There are many people who don't know what to do with their lives. 1 2 3 4 5  EF
19. Most people don't realize how much their lives are controlled by plots hatched in a secret by others. 1 2 3 4 5  EF
20. People feel affectionate towards me. 1 2 3 4 5  EF
21. I would say I nearly always finish things once I start them. 1 2 3 4 5  EF
22. When I make plans ahead, I usually get to carry out things the way I expected. 1 2 3 4 5  EF
23. I think most married people lead trapped (frustrated or miserable) lives. 1 2 3 4 5  EF
24. It's hardly fair to bring children into the world the way things look for the future. 1 2 3 4 5  EF
25. Some people feel as if other people push them around a good bit and I feel this way too. 1 2 3 4 5  EF
26. I am usually alert. 1 2 3 4 5  EF
27. Nowadays a person has to live pretty much for today and let tomorrow take care of itself. 1 2 3 4 5  EF

SECTION C: This section contains some questions on general health and on your social activities.

28. How would you say your health is today? Would you say your health is: (Circle your answer)  SF
   1. VERY GOOD
   2. PRETTY GOOD
   3. NOT TOO GOOD

29. Taking all things together, how would you say things are today? Would you say you are:  SF
   1. VERY HAPPY
   2. PRETTY HAPPY
   3. NOT TOO HAPPY
30. In general, how satisfying do you find the way you're spending your life today? Would you call it:

1. COMPLETELY SATISFYING
2. PRETTY SATISFYING
3. NOT VERY SATISFYING

31. How would you say your physical functioning is today? (By this we mean the ability to move around, see, hear and so forth)

1. GOOD
2. GOOD TO FAIR
3. FAIR
4. FAIR TO POOR
5. POOR

32. How would you say your social functioning is today? (By this we mean working with others, getting along with friends or family)

1. GOOD
2. GOOD TO FAIR
3. FAIR
4. FAIR TO POOR
5. POOR

33. How would you say your emotional functioning is today? (By this we mean your ability to remain in good spirits most of the time, and to be usually happy and satisfied with your life). (Circle your answer)

1. GOOD
2. GOOD TO FAIR
3. FAIR
4. FAIR TO POOR
5. POOR

34. What is your occupational status? (Check all that apply)

1. WORK FULL-TIME (for WAGES)
2. WORK PART-TIME (for WAGES)
3. ON VACATION
4. RETIRED
5. ON SICK LEAVE
6. A STUDENT
7. A HOUSEWIFE
8. OTHER (please specify):

35. How much time in a one week period, do you usually spend watching television?

1. TWO HOURS OR MORE A DAY
2. LESS THAN TWO HOURS PER DAY BUT MORE THAN ONE HOUR
3. LESS THAN ONE HOUR PER DAY BUT MORE THAN THREE HOURS PER WEEK
4. LESS THAN THREE HOURS PER WEEK
5. NONE
36. Which of the following describe your usual social and recreational activities? 

a. going to church?
   1. NO
   2. YES

b. going to a relative's home?
   1. NO
   2. YES

c. any other activities? (please specify)

37. Has anyone visited you in the last week? (Circle your answer)

a. a relative?
   1. NO
   2. YES

b. a friend?
   1. NO
   2. YES

c. a religious group member?
   1. NO
   2. YES

d. a social agency representative? (for example, welfare, mother's allowance, workmens compensation board, Victorian Order of Nurses),
   1. NO
   2. YES

38. Do you have a telephone?
   1. NO → GO TO Q.40
   2. YES

39. Have you used your telephone in the last week to call:

a. a friend?
   1. NO
   2. YES

b. a religious group member?
   1. NO
   2. YES
39. Cont'd

c. a social agency representative? (for example, welfare, mother's allowance, workmens compensation board, Victorian Order of Nurses)

   1 NO
   2 YES

40. Have you been called in the last week by a social agency representative? (for example, welfare, mother's allowance, workmens compensation board, Victorian Order of Nurses)

   1 NO
   2 YES

41. How long has it been since you last had a holiday? (Write-in number "0" if presently on holidays).

   MONTHS OR YEARS

42. During the last year, have any of the following things happened to you:

a. separation from your spouse?

   1 NO
   2 YES

b. divorce?

   1 NO
   2 YES

c. gone on welfare (or received monies from unemployment insurance, workmens compensation or mother's allowance)?

   1 NO
   2 YES

d. trouble getting along with friends/relatives during the last year?

   1 NO
   2 YES

e. retired from work during the last year?

   1 NO
   2 YES

f. some other problem or change in your life?

   1 NO
   2 YES
43. As part of this research project, we would like to contact one person who is close to you and would be familiar with your everyday health (such as a relative or a close friend).

May we have your permission to hold a short telephone interview with the person you select, to ask about his/her impression of your health?

1  NO
2  YES

Name of this person:

______________________________

please print

Address:

______________________________

Phone Number: __________________

Relationship to you:

______________________________

THANK YOU VERY MUCH FOR YOUR HELP IN THIS STUDY
APPENDIX VI

Rating of Perceived Exertion Scale
Rating of Perceived Exertion Scale

0  Nothing at all
0.5 Very, very light  (just noticeable)
1  Very light
2  Light  (weak)
3  Moderate
4  Somewhat heavy
5  Heavy  (strong)
6
7  Very heavy
8
9
10 Very, very heavy  (almost maximum)

0  Maximal
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