THE EFFECT OF A PHYSICAL TRAINING PROGRAMME ON EXERCISE-INDUCED ASTHMA

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DECLARATION

I, Jonathan King, declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that no part thereof has been, is being, or is to be submitted for another degree at this or any other university.

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ABSTRACT

Physical training has become an integral part of the management of asthmatic subjects. However, only a handful of studies have shown an increase in fitness measured as an increase in maximal oxygen consumption (vO_2 max) in asthmatics in response to training. Some investigators have suggested a causal relationship between improved physical fitness and reduced exercise-induced asthma (EIA), but many have found no change in EIA in response to training. This study investigated the trainability of atopic asthmatic boys aged 9-14 years. Maximal oxygen consumption (vO_2 max), maximal treadmill performance, heart rate at submaximal exercise, the blood lactate turnpoint and the effect of a training programme on the severity of EIA were investigated. The status of clinical asthma was also monitored.

Fourteen subjects initially participated in the study and 2 were excluded because study requirements were transgressed. Six subjects were trained bi-weekly for 12 weeks and 6 subjects formed the control group. The following investigations were performed on all subjects: Lung function tests (peak expiratory flow rate [PEFR], forced expiratory volume in 1 second [FEV1], maximal mid-expiratory flow rate [MMEF] and forced vital capacity [FVC]) were performed before and after individually standardized asthmagenic treadmill tests in March, July and December (1985). Maximal oxygen consumption (vO_2 max) and blood lactate concentrations were determined during an incremental treadmill run before and after the trial period (September-December 1985). Clinical status of asthma was assessed from questionnaires, diary scores and medication prescribed at the Red Cross War Memorial Children's

Hospital, Allergy Clinic. Duration and intensity of training sessions were optimized with the use of inhaled sodium cromoglycate powder (Lomudal, Fisons) and fenoterol hydrobromide aerosol (Berotec, Boehringer Ingelheim). Additional medication was prescribed at the discretion of the respective paediatricians at the Red Cross War Memorial Children's Hospital, Allergy Clinic.

The exercise group showed significant improvements in several indicators of fitness measured during incremental treadmill testing after the training programme: absolute vO_2 max (paired t-test: $p=0.003$), relative vO_2 max ($p=0.01$) and maximal treadmill speed reached ($p=0.04$). In response to training, a significant decrease in heart rate ($p=0.02$) was noted in the trained group at a given speed in the submaximal asthmagenic treadmill run. None of these variables improved significantly in the control group. The blood lactate concentrations and lactate turnpoints during maximal treadmill exercise, and lung functions in response to the asthmagenic treadmill tests did not change significantly after the trial period in either group. All trained subjects, but no subjects in the control group, reported using less inhaled medication after the trial period. Meaningful analysis of daily diaries was not possible because of poor compliance in completing the diaries.

The main finding was that boys with moderately severe asthma can be physically trained and show an improvement in vO_2 max and other indicators of cardiovascular fitness without adverse effect on EIA. Useage and presciption of medication was decreased in the trained group after the trial period, thus presenting subjective, but no objective evidence of improved lung function.

ABBREVIATIONS

a-v	Arteriovenous
AES	Air entry score
BR	Breathing reserve
$CaSo_2$	Calcium Sulphate
COAD	Chronic obstructive airways disease
cm	centimetre
CO_2	Carbon Dioxide
Co	Company
EIA	Exercise-induced asthma
$FeCo_2$	Fraction of Carbon Dioxide in expired air
FeO_2	Fraction of Oxygen in expired air
FEV1	Forced expiratory volume in one second (1)
FRC	Functional residual capacity
FRG	Federal Republic of Germany
FVC	Forced vital capacity
hr	hour
HIA	Hyperventilation-induced asthma
HRR	Heart rate reserve
HRmax	Maximal heart rate
HRrest	Resting heart rate
Inc	Incorporated
Ind MVV	Indirectly measured maximal voluntary ventilation
l	litre
kg	kilogram
km	Kilometre
LDH	Lactate dehydrogenase
LI	Lability Index
Ltd	Limited
m	metre

mg	milligrams
min	minute
ml	millilitre
mM	millimole
MMEF	Maximal mid expiratory flow rate ($l\ min^{-1}$)
nm	nanometres
NAD	Nicotinamide adenine dinucleotoide
NCHS	National Centre of Health Statistics (USA)
O_2	Oxygen
PCA	Perchloric acid
pCO_2	Partial pressure of Carbon Dioxide
Pe	Pennsylvania
PEFR	Peak expiratory flow rate
PFK	Phosphofructokinase
pO_2	Partial pressure of oxygen
RAST	radioimmunosorbent test
RER	Respiratory exchange ratio
RPM	revolutions per minute
sec	second
SGaw	Specific airways resistance
SRS-A	Slow reacting substance of anaphylaxis
Std	Standard
SD	Standard deviation
SE	Standard error of the mean
TGV	Thoracic gas volume
UK	United Kingdom
USA	United States of America
vCO_2	Carbon Dioxide output (unit volume per minute)
$vCO_{2\ max}$	Maximal Carbon Dioxide output (Written as vCO2max in tables)

Ve	Expiratory ventilation
Vemax	Maximal expiratory ventilation
$\dot{V}O_2$	Oxygen uptake (unit volume per minute)
$\dot{V}O_{2\,max}$	maximal Oxygen uptake (Written as vO2max in tables)
$B\ min^{-1}$	Beats per minute (also B/min in the tables)
$km\ h^{-1}$	kilometers per hour (km/h in the tables)
$l\ min^{-1}$	litres per minute (l/min in the tables)
$mg\ kg^{-1}\ min^{-1}$	milligrams per kilogram per minute (mg/kg/min in the tables)
$mmol\ l^{-1}$	millimoles per litre (mmol/l in the tables)

CHAPTER I

RATIONALE AND SCOPE OF THE THESIS

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INTRODUCTION TO THE PROBLEM

The attitude of many medical doctors towards exercise and chronic illnesses has been notoriously conservative. Bronchial asthma is a typical chronic illness and is often associated with considerable morbidity. The advent of bronchodilator therapy has done much to allow asthmatics to lead more 'normal' lives. Despite the advances in pharmacological therapy many asthmatics, especially children, are excluded from participating in sports for fear of precipitating an asthmatic attack.

Physical activity and play is part of the daily lives of most children and exclusion from exercise can lead to a reduction in their main form of socialising. It seems logical that asthmatic children should be assisted by all methods possible to participate more fully with their own society in order that they show 'normal' physical, emotional and social development.

Control of clinical asthma is obligatory and should allow a child to cope better with his or her illness. This should facilitate participation in the energetic lifestyle which many children lead. Parental attitude towards exercise is important and children should neither be forced to nor prohibited from participating in physically active pursuits. An important point is that for most asthmatics, exercise intolerance is a result of hypoactivity which is incidental to the disease, rather than as a direct result thereof (Bar-Or, 1986).

Asthmatic episodes are characterised by breathing difficulty and early investigators used breathing exercises to control or abort

these events or both (Baker, 1951; Livingstone, 1952). The basic aim was to improve respiratory function through training of thoracic musculature. Limited success was obtained and the most effective training involved strenuous respiratory manoeuvres which proved to be impractical and boring (Belman, Thomas and Hawksworth, 1985).

Physical conditioning was introduced to training programmes and this soon became an accepted mode of therapy for asthmatics (Millman et al , 1965; Itkin and Nacman, 1966). Initial training programmes involved callisthenics and mildly strenuous exercises which did not result in objective improvement in physical fitness. Only recently have more strenuous training programmes been introduced (swimming training: Fitch, Morton and Blanksby, 1976; distance running: Nickerson et al, 1983).

In order to understand the rationale behind exercise training in the rehabilitation of patients with chronic obstructive airways disease (COAD), one needs to consider the factors limiting ventilation in these patients and the physiological changes which accompany exercise training. Celli et al (1986) described the difficulties that patients with severe COAD encountered when performing unsupported arm work. The shoulder girdle muscles are also involved in breathing, unlike normal subjects and the accessory muscles of respiration become overloaded. These patients are unable to sustain effective ventilation and they experience the early onset of dyspnpoea. Diminished elastic recoil and hyperinflation of the lungs flatten the diaphragm and place it at a mechanical disadvantage, thus reducing its contribution to inspiratory effort (Roussos and Macklem, 1977). In those with the worst COAD, Celli and co-workers found that the

ventilatory demands of arm exercise led to dyssynchronous movements of the abdomen and chest wall.

Methods of relieving dyspnoea in those with COAD should aim to increase ventilatory capacity or to decrease the ventilatory requirement for a given work load, or both. Specific training of the ventilatory muscles has been successful in achieving the former objective and training the muscles of locomotion should help to achieve the latter. For asthmatics, use of appropriate medication plays an important role in preventing bronchospasm during training sessions.

Biochemical adaptation of skeletal muscle in response to training has been well documented (Davies, Packer and Brooks, 1981; Holloszy and Coyle, 1984). In response to exercise training, the trained muscle shows increases in the number of mitochondria and in the concentrations of enzymes involved in oxidative metabolism. Furthermore, capillarity of trained muscle increases. This results in a more complete extraction of oxygen from the circulation. Strenuous exercise of progressively increasing intensity requires ATP production at a rate exceeding that which oxidative metabolism can provide. Oxygen-independent metabolism (glycolysis) plays an increasingly important role under these conditions but is limited by the onset of acidosis which accompanies muscle and blood lactate accumulation during exhaustive exercise at high intensity. Exercise training delays the onset of muscle and blood lactate accumulation, thus allowing a higher workload to be reached before this type of fatigue occurs. The workload which immediately precedes that at which blood lactate accumulation begins is termed the 'lactate turnpoint'. The lactate turnpoint provides an objective measure of endurance

fitness.

Training also results in a lower heart rate and pulmonary ventilation at any given submaximal workload. Improvement of these variables is commonly referred to as 'improved cardiovascular or cardiopulmonary fitness'.

An important pre-requisite for successful exercise training in those with COAD or asthma is that ventilatory limitation (bronchospasm) should not restrict exercise capacity to levels below which a training effect is produced. Exercise intensity needs to be near the 'lactate turnpoint' for optimal training. Cycle-ergometer training in non-asthmatics can result in decreased lactate production at a given intensity of heavy exercise, which in turn can reduce the ventilatory requirements at that workload (Casaburi and co-workers, 1986). Successful training is usually demonstrated by attainment of a higher workload on laboratory apparatus (treadmill or cycle ergometer). This is usually accompanied by an increase in maximal oxygen consumption (vO_2 max) which is due to an increase in cardiac output and arterial venous oxygen difference. This measurement has become a traditional measure of endurance fitness.

Only a handful of studies have shown an increase in maximal oxygen uptake (vO_2 max) in asthmatic children in response to a training programme (Itkin and Nacman, 1966; Bundgaard et al, 1982; Orenstein et al, 1985; Ramazanoglu and Kraemer, 1985). A fault of studies which have failed to show this improvement is that the training sessions were of inadequate intensity or frequency or both (Chai et al, 1967; Vavra et al, 1971).

The pulmonary response of an asthmatic to exercise is

reproduceable and has been well documented (see literature review). In asthmatics, mild bronchodilatation usually occurs after about 2 to 3 minutes of continuous exercise. Subsequent bronchoconstriction may force an asthmatic to stop exercising after several minutes, but a characteristic feature is the development of airways obstruction after stopping exercise. This phenomenon is referred to as exercise-induced asthma (EIA). The index most commonly used in quantifying EIA is the percent post-exercise fall from pre-exercise baseline in FEV1. Those with mild disease may be able to 'run through' the asthmatic episode, continue exercising without distress and experience reduced asthma afterwards. The nature of EIA is discussed more fully in the literature review.

Improved cardiovascular fitness should result in lower ventilatory requirement for a given submaximal workload in trained asthmatic subjects. The degree of EIA has been shown to be proportional to heat or water loss from the respiratory tract (Deal et al, 1979b; Anderson et al, 1982, 1983, 1984; Eschenbacher and Sheppard, 1985). It follows that the degree of ventilation determines these losses for given ambient conditions. Reduction in the stimulus for EIA through reduction in the ventilatory load should thus result in improved exercise tolerance in asthmatics. Clinical observation has led to the speculation that improved fitness is associated with a reduction in EIA and improved clinical asthma. Several researchers have shown this experimentally (Oseid and Haaland, 1978; Henriksen and Neilsen, 1983; Arborelius and Svenonius, 1984) but the mechanism whereby exercise produces this effect is not established. Most subjects used in these studies had mild asthma and improvement in EIA was invariably accompanied by improved cardiovascular fitness or

working capacity or both. However, most researchers addressing this issue have found no change in EIA in response to a physical training programme (Itkin and Nacman, 1966; Hyde and Swarts, 1968; Fitch et al 1976); Schnall et al, 1982; Bundgaard et al, 1982; Nickerson et al, 1983). These inconsistent results prompted me to re-investigate the effect of a physical training programme on EIA.

STATEMENT OF THE PROBLEM

A review of the relevant literature reveals that previous investigators have had varying ideas about training asthmatic children. It is also remarkable that documented use of pre-medication prior to training sessions has become a recent feature (Henriksen and Neilsen, 1983).

A major problem with many of the earlier studies was that the training programmes were of insufficient intensity to induce a training effect. It seems that the asthmatic subjects were exercised relatively conservatively in order to prevent an asthmatic episode. It is generally accepted by exercise physiologists that cardiovascular fitness improves in proportion to intensity and frequency of training. The logical question which follows is whether it possible to have the subjects train at a sufficiently high intensity to show an improvement in fitness as measured by vO_2 max knowing that airways obstruction is their main limitation to exercise.

Knowing the capriciousness of asthma, it seemed (before the study began) that a large improvement in EIA or clinical asthma was needed before a definite conclusion could be reached. This posed statistical problems with the small sample group.

Further problems arose which were unique to this study. There were times when I thought that I would have to abandon the project due to circumstances beyond my control. Some of these problems are listed below. The first two points were particularly important as most subjects relied on public transport exclusively.

i) Political unrest in the townships made commuting dangerous at times.

ii) Bus services to the townships were withdrawn on a number of occasions.

iii) The training sessions were held outdoors only when the weather was fine. Indoor training proved to be an exercise in discipline! Fortunately, almost all the sessions were held outdoors.

iv) During Ramadan (most of June 1985), Moslem subjects invariably did not take their medication during the daylight hours if they could help it. This complicated the laboratory testing schedule and most subjects were tested when the fast was over. There were Moslem subjects in both groups and I assumed that the change in medication useage affected the clinical asthma of both groups equally.

SCOPE OF THE STUDY

Twelve subjects divided equally into an exercise and control group participated in the study which was conducted from March to December 1985. Identical measurements were made in all subjects before and after a three month trial period, during which the exercise group was trained. Pulmonary function tests were

performed before and after an individually standardised exercise treadmill run before the trial period on two occasions: soon after the initial screening test (March) and in July. During the trial period (September to December) the exercise group participated in a physical training programme while no new intervention was instituted in the control group. Maximal exercise capacity was determined in each subject on a motor driven treadmill before the trial period. Identical asthmagenic and maximal treadmill tests were performed after the trial period.

Clinical asthma was monitored by having all subjects complete a daily diary.

LIMITATIONS OF THE STUDY

A major limitation in the study is the small sample size, thus lowering the level of confidence which can be placed on the results. The eventual number of subjects was largely due to the difficulty in recruiting subjects (see 'methods, selection criteria'). Most subjects relied on public transport and the practicalities of regular commuting excluded a large number of prospective subjects.

The asthmagenic treadmill protocol required the subjects to run for six minutes at a speed which produced a heart rate of 80% of the age predicted value. Not all the subjects were able to maintain the required workload and this made inter-subject comparisons difficult.

Severe post-exercise bronchoconstriction in a number of subjects did not allow them to complete successfully a spirometer manoeuv-

re lasting 6 seconds. The percentage fall for FEV1, MMEF and FVC was recorded as 100% in these instances and these values skewed the distribution of results. The limitation introduced by this problem is that assumptions made in the application of statistical tests are violated.

Each subject was given a diary sheet which they had to complete daily at home. In retrospect, this was not a good idea as the compliance decreased with time.

PURPOSE OF THE STUDY

The main purpose of the study was to devise a training programme specifically for asthmatic children. I felt that the most important aim was to educate the children, through regular exercise sessions, to become adapted to a more physically active lifestyle while still being aware of their asthma. The use of prophylactic medication before exercise was reinforced at every training session.

The subjects were allowed to bring their friends to the training sessions. I felt that this would more closely simulate spontaneous play in non-supervised situations.

Furthermore, I wanted the programme to succeed on a small budget: apart from laboratory costs, the main regular expenditure was busfare for the children. Since all published studies of this nature have been conducted in First World countries where infrastructure is more sophisticated and medical facilities are more easily accessible, I conducted what turned out to be a pilot study investigating the practicalities of a similar progamme in a Third World situation.

CHAPTER II

LITERATURE REVIEW

1. INTRODUCTION TO LITERATURE REVIEW

In a detailed review of exercise-inducd asthma, Sandra Anderson and co-workers (1975) acknowledge that the first detailed descriptions of EIA were published in the late seventeenth century by Willis (1684) and Sir John Floyer (1698) but little research was done on this subject until recently. In order to obtain a perspective of research findings and to give the many investigators credit for their contributions, it is useful to follow developments in historical sequence.

The first section of the literature review deals with early findings, the nature and standardisation of tests used to provoke EIA. The main part of the review presents a history of the development of physical exercise programmes for asthmatic persons. The final part discusses research into the initiating stimulus for EIA. Although I have not investigated this in the study, I have included it because this has become the current and controversial direction of research in EIA. I have highlighted what I consider to be the main findings of researchers in this field.

2.THE NATURE OF EXERCISE-INDUCED ASTHMA.

2.1 Early Findings

The first documented evidence of exercise-induced asthma originated from Artaeus the Cappadocian (East Asia Minor) who, in the second century wrote : 'If from running, gymnastic exercises, or any other work the breathing becomes difficult, it is called asthma...'. The word 'Asthma' has middle eastern origins, and is derived from the (14th century) Greek word 'azein', which means 'to breathe hard' (Collins English Dictionary).

No other reference to EIA is found in the Western literature until the seventeenth century when Willis and Floyer published their findings. Sporadic reports appeared until the twentieth century, which marked the beginning of modern research into EIA. The following quotes are from a comprehensive review on EIA by Anderson and colleagues (1975) :

Willis (1684) wrote: 'Whatsoever therefore makes the blood boyl, or raises it into an effervesence as violent motion of the body or mind, excess of extern cold or heat, the drinking of wine, vinery, yea sometimes meer heat of the bed doth cause asthmatical assaults to such as are predisposed.'

In his publication 'A Tretise of the Asthma' Floyer (1698) wrote: 'All violent exercise makes the asthmatic to breathe short; because their lungs are frequently opressed with tubercula; and if the exercise be continued, it occasions a fit, by putting the spirits to great Expansion.... The most agreeable exercise is riding, ringing of a dumb bell, swinging, dancing: walking is more vehement than riding, but not so great as the other; those exercises that move the arms, exercise the lungs most.' This

English physician was an asthmatic and could therefore authoritatively write on the subject based on his personal experience. Contrary to previous reports, Thorowgood (1873) noted that in some asthmatics mild exercise could abort an impending attack of asthma. Livingstone (1935) suggested that 'bronchioles were narrowed by spasm and congestion', and that lung hyperinflation occurred during an asthma attack. The author suggested breathing exercises in order to 'empty the lungs...re-educate the automatic diaphragm movements.' A trial of these exercises prescribed by Livingstone for 1 year yielded results similar to those produced by avoidance of allergens.

In 1946 Herxheimer measured vital capacity in 6 patients who develped EIA and hyperventilation-induced asthma (HIA). The subjects exercised or hyperventilated at rest for 2 to 4 minutes. His observations led to the speculation that bronchospasm 'never develops during the exercise' and concluded that 'excess hyperventilation during recovery' was the cause for the asthmatic attack after exercise. He further suggested that excess CO_2 loss and subsequent pH shift were triggering factors. These theories were later shown to be incorrect.

During the following decade conflicting reports appeared concerning the effect of exercise on lung function. Experimental protocols varied, and it became apparent that results depended on whether observations were made during, or after the exercise bout. The different types of exercise used added further variation to the studies.

In 1962 Jones, Buston and Wharton noted these previous reports :

i) Capel and Smart (1959) reported an increase in FEV1 in asthmatic subjects within 5 minutes of the end of an

exercise bout.

ii) Engstrom et al (1960) measured lung compliance and airways resistance during and after exercise. The authors obtained variable results for both periods of data collection.

They therefore determined to study the effects of exercise duration on ventilatory function. The authors noted that running for 1-2 minutes resulted in an increase in FEV1, and that more prolonged running (8-12 minutes) was followed by a fall in FEV1. The results were thought to reflect bronchodilatation followed by bronchoconstriction. They concluded that both the duration and intensity of exercise determined the nature of the ventilatory changes. The authors, however, admitted that no attempt was made to standardise the exercise intensity in the study. It was also shown that pretreatment with inhaled isoprenaline sulphate aerosol diminished both the increase and decrease in FEV1 after short and long duration exercise respectively.

The following year the same authors conducted a more elaborate study based on their previous work, and came to three main conclusions. They showed that both short and long duration running tests :

i) were diagnostic of asthma so that a negative result should lead to a re-appraisal of the diagnosis.

ii) were useful for assessing severity of the disease.

iii) were useful in evaluating the drugs to prevent EIA.

The authors also suggested that short bursts of exercise were the most suitable for asthmatics, but that bronchospasm could still occur despite the asthmatic performing intermittent exercise.

In 1966 McNeill et al observed that EIA could develop in asthmatics who had normal baseline lung function. A comparative drug trial was conducted and prior parenteral administration of atropine, hydrocortisone, mepyramine maleate, and chlorpromazine failed to inhibit EIA. At that stage beta-2 agonist drugs, in particular adrenaline, remained the gold standard for the prevention of EIA.

The authors speculated that the 'exercise effect is either reflex or humoral in origin' ; the possible humoral factors were thought to be histamine, 5-hydroxytryptamine, slow-reacting substance of anaphylaxis (SRS-A) or bradykinin.

It is interesting to note that in a letter to the British Medical Journal in 1969, Ward, Gomes and McNeil reported that inhalation of sodium cromoglycate powder immediately before running up and down stairs reduced the degree of EIA, in agreement with the findings of Davies (1968). The authors however, did not think that this would prove a viable form of treatment. One could speculate whether sodium cromoglycate would have been accepted sooner as a form of treatment for EIA had Ward and colleagues been more optimistic.

The search for the stimulus for EIA began to gain momentum in the nineteen sixties. Rebuck and Read (1968) showed a decrease in FEV1 after hyperventilation with CO_2. Their hypothesis was based on the study of a severe asthmatic who was hypoxic and hypercarbic at rest; relative hypocapnoea occurred after brief hyperventilation. They suggested that hypocapnoea after exercise might be a common abnormality which may play a role in initiating bronchospasm (with or without 'mechanical reflexes' playing a role).

In 1969 Seaton et al measured arterial pH, pCO_2, pO_2, lactate, and pyruvate in response to hyperventilation at rest, and exercise. They speculated that metabolic acidosis could trigger the release of substances such as bradykinin or SRS-A , thus initiating bronchospasm. A post-exercise fall in FEV1 was associated with a metabolic acidosis in all three subjects studied, but a fall in pH in response to hypercapnea was not associated with a fall in FEV1. Furthermore, prevention of post-exercise arterial acidosis by infusion of intravenous sodium bicarbonate did not prevent EIA. These results are therefore not consistent with their hypothesis.

Fisher et al (1970) reported the first study using two forms of exercise to determine whether hypocapnea or cholinergic mechanisms played a role in EIA. Both forms of exercise were not standardised, and the authors could not explain why stairway climbing caused greater increases in airways resistance than did exercising on a cycle ergometer. It was also observed that inhalation of CO_2 reduced airways resistance; this was interpreted to mean that hypocapnea could cause airways obstruction in asthmatics. Intravenous atropine sulphate protected against an inhaled histamine challenge, but failed to prevent EIA; this suggested that cholinergic pathways did not contribute to EIA.

Some of these points were confirmed when Fitch and Morton (1971) reported the first comparative trial of the effect of different exercise modes on EIA. The authors demonstrated that treadmill running and cycling on an ergometer produced greater EIA than did swimming. The protocol was standardised with respect to exercise duration and exercising heart rates. Problems in interpreting the study were that 8 of 40 subjects maintained their prescribed

medication and that the warm humid environment above the (indoor heated) swimming pool could have attenuated the asthmatic response.

This study established that the exercise protocol used for provoking EIA needeeded to be standardised before meaningful comparisons could be made between studies. However, issues such as characterising the nature of EIA, finding the initiating stumulus for EIA and the investigation of drug modifications of EIA seemed to enjoy a higher priority in the investigators' thoughts.

In 1971 Chan-Yeung et al investigated the ventilatory response to cycling on an ergometer, and to hyperventilation. The protocol was loosely standardised and only 3 of 7 subjects developed EIA. Higher ventilation was reached during the hyperventilation tests and all subjects showed a fall in FEV1 of greater than 10% of the baseline value. The degree of fall in FEV1 was proportional to the minute ventilation during hyperventilation; this seemed to explain why previous investigators had failed to demonstrate HIA (McNeill et al 1966; Hafez and Crompton 1968) as they had used low ventilation rates. Despite unmatched ventiatlon rates in the two tests, the authors tentatively postulated that EIA was synonymous with HIA. The authors found no correlation between venous lactate levels, arterial blood gas levels and EIA and rejected contrary findings by Newhouse et al (1964), and Fisher et al (1970). Repeated exercise tests after 2 hourly intervals resulted in diminishing EIA in an adult subject; this prompted speculation that 'bronchoconstricting substances' (BS) released during exercise and during hyperventilation at rest were the cause of airways obstruction. The rationale behind this popular

theory is that BS are released in response to exercise and that 2-3 hours are needed for the regeneration of these substances. Exercise during the refractory period results in release of a smaller amount of BS, with a concomitant lesser degree of EIA.

In 1971 Anderson et al investigated bronchial lability after free running, treadmill running and cycling on an ergometer. This was the first trial where ventilation was standardised for all exercise modes. The results confirmed the authors' clinical impression that running caused greater bronchoconstriction in asthmatics than did cycling . It was speculated that the subjects actually did more work for the same O_2 consumption during running compared with cycling (because of more 'negative work'). Lower respiratory exchange ratios (RER) during running appeared to correlate with bronchial lability and higher heart rates in asthmatics. The authors did not acknowledge that these variations may have influenced their results.

The authoritative study which led to standardisation of the asthmagenic treadmill test was done by Silverman and Anderson in 1972. A series of experiments revealed that post-exercise bronchoconstriction was maximal when running exercise lasted 6-8 mins at a gradient of 10-15 % , corresponding to 60-85 % of the subjects' vO_2 max ; and was greater after running than after walking at the same rate of O_2 consumption.

The reproducibility of an asthmagenic treadmill test was also investigated by calculating the coefficient of variation of the percentage fall in PEFR for different time intervals (eg hours, days, weeks) :

coefficient of variation = (Standard deviation/mean % fall) x 100

It was found that the coefficient of variation was least (21%) when tests were repeated within one week and greatest (53%) for tests repeated at monthly, or yearly intervals. The refractory period described by McNeill (1966) and Chan-Yeung et al (1971) was not found in 8 subjects who exercised repeatedly at 2 hourly intervals. This study therefore established a standardised exercise protocol which would produce optimal results and could be used for future drug trials.

In 1973 Godfrey, Silverman and Anderson reviewed previous studies on the nature of EIA and continued their studies using larger sample sizes. Subjects were required to cycle on an ergometer, run around the hospital and swim in a heated pool. All exercise was designed to raise the heart rate to at least 170 beats per minute (65-85% maximal working capacity) for 6 minutes. Drug studies and repeated testing during the course of the day were performed. The authors confirmed their previous findings and showed that the exercises could be categorized in the following sequence based on their increasing asthmagenicity at the same relative work load in asthmatic subjects: walking < swimming < ergometer cycling < treadmill running < free running. EIA was abolished by inhalation of salbutamol aerosol (0.2 mg), and for a shorter duration, by isoproterenol aerosol (0.16mg). Varying degrees of protection was afforded by sodium cromoglycate.

It was evident that the variety of responses to different types, severities and durations of exercise made individual case reports of limited value (Crompton 1968; Rebuck and Read 1968; Herxheimer 1946 & 1972). Uncontrolled trials and poor experimental designs were open to criticism. The authors concluded that it was unlikely that any single factor such as hyperventilation,

hypocapnea, lactic acidosis, acidaemia or change in arterial oxygen tension was solely responsible for EIA. They reassessed their position on the refractory period of EIA and acknowledged that this could occur if successive tests were conducted within short intervals of less than 1.5 hours.

2.2 Criteria for EIA

Many earlier investigators used arbitrary criteria to decide whether or not a subject developed EIA. It was not until non-asthmatics were studied that more rigid criteria were applied. In the 1960's investigators found that in non-asthmatics, PEFR and FEV1 fell 8-14% from the resting value after an exercise test.

In 1970 Sly reported that almost half of 116 asthmatic children showed at least a 10% drop in PEFR after 8 minutes of inclined treadmill walking. This incidence, which was less than that obtained by Jones (1963), was probably due to the relatively lower intensity of the exercise. Sly also found a negative correlation between pre-exercise PEFR and the increase in PEFR at 2 minutes of exercise; that is the lower the baseline value, the greater the bronchodilatation with short-duration exercise.

These criteria assumed more importance when the asthmagenic treadmill test was standardised by Silverman and Anderson (1972). The following year the same authors found the upper limit (mean + 2 standard deviations) of the percentage fall in PEFR to be 10% in non-asthmatic children (Silverman and Anderson, 1972), and 9% in non-asthmatic adults (Anderson, 1972 cited by Anderson et al, 1975). In a sample of 97 asthmatic children who performed a treadmill test, the percent fall in PEFR was greater than 2

standard deviations above normal in 70 % of the subjects.

Godfrey (1974) reviewed 68 asthmatic children who had a normal first exercise test. For the second test he found that the percent fall in PEFR was abnormal in 87% of cases, and exercise lability (% fall + % rise) was abnormal in a further 10%. This meant that 97% of asthmatics could be shown to have abnormal bronchial lability either on the first or second test. This agreed with Jones (1966) who maintained that virtually all asthmatics should develop EIA, so that two or more negative tests places the diagnosis in doubt.

2.3 Mode of exercise and EIA

Anderson and co-workers (Anderson, Connolly and Godfrey, 1971; Anderson, Silverman and Walker, 1972) found that running resulted in greater EIA than cycling when both were performed at comparable heart rates. However, Miller et al (1975) found similar falls in PEFR in subjects who ran and cycled at the same rate of oxygen consumption. The authors did not favour the cycle ergometer as a stimulus for EIA because the relatively smaller muscle mass employed led to the early development of local muscle fatigue.

Eggleston (1975) favoured the cycle ergometer for practical reasons but did not recommend it for drug trials or epidemiological studies (because of the lower asthmagenic potential). Pierson and Bierman (1975) had a more clinical approach and gave the following reasons for free running to be the stimulus of choice: it stimulated the 'normal exercise pattern' of children and minimal equipment was necessary. Environmental factors were considered to be additional stimuli. The authors did not discuss

the problems of comparability, nor the standardisation of exercise intensity.

Other exercise modes were studied by Fitch (1975); treadmill running produced the most EIA whereas swimming produced the least. Bicycle and kayak ergometer exercise produced intermediate degrees of bronchoconstriction. Fitch gave no details concerning the different exercise protocols, nor the environmental conditions.

Shapiro et al (1979) found that free running and treadmill exercise to a pulse rate of 180 beats per minute produced greater degrees of EIA than did treadmill running to a pulse rate of 170 beats per minute. In the samples studied, the incidence of EIA was slightly higher with free running compared to the faster treadmill protocol.

In a more carefully controlled study, Inbar et al (1981) found that the post exercise fall in FEV1 was significantly greater after running compared with swimming. Ventilation, oxygen consumption and tidal volume were matched for the last two minutes of exercise only, and the heart rate was greater during running (180 beats per minute) compared with swimming (165 beats per minute). Thus, the total oxygen consumption (work done) could have been higher during the running exercise, and this might explain the results obtained. The high humidity and high ambient temperature (heated pools) associated with swimming should be sufficient to protect most asthmatics against EIA. Inbar et al (1980) investigated this and found that EIA was prevented when dry or humid air was inhaled during tethered breaststroke swimming. A more rigorous comparison was done by Bar-Yishay and the

above authors (1982). In addition to the previous findings, it was demonstrated that respiratory heat loss was similar for both modes of exercise. Many clinicians and researchers believe that the degree of EIA is proportional to the degree of heat loss from the airways. If this hypothesis is valid, the severity EIA should be similar for a given amount of heat loss irrespective of mode of exercise. Bar Yishay et al (1982) found that treadmill running resulted in greater EIA than did swimming. A possible confounding factor in both studies was that the average heart rate reported was higher for a screening treadmill test compared with the swimming test. Considering the abovementioned hypothesis, it appears that there is a small difference in the asthmagenicity of the two modes of exercise which is unexplained by respiratory heat loss.

For diagnostic or epidemiological purposes free running remains the exercise of choice eliciting EIA. Where more controlled conditions are required (eg. for assessment of asthmatic or atopic athletes, longitudinal comparisons, drug trials etc.) treadmill running is preferred. The bicycle ergometer is advantageous if invasive procedures are to be performed during exercise or if portability is desireable.

2.4 Standardisation of exercise testing

Cropp (1979) was one of the first investigators to recommend guidelines for the evaluation of the ventilatory response to exercise. He proposed that:

i) Protocols should be age adjusted.

ii) In subjects under 25 years the work rate should be rapidly raised to 85% of the predicted maximum.

iii) Subjects should breathe through the mouth.

iv) Strict safety measures should be employed.

The author abbreviated his scoring system and included pulmonary function measurements to quantify the severity of EIA. This system however, did not become widely used.

A detailed set of guidelines for the methodology of exercise testing of asthmatics was published in the same year by Eggleston, Rosenthal, Anderson and co-workers (1979); Cropp was also an author. These guidelines clarify procedures for a standardised method of evaluating airways response and deserve mention as they are followed by most researchers today. They are described in the folowing sections.

2.5 Selection and preparation of subjects

All subjects should be evaluated by a physician prior to exercise and a rhythm ECG should be included. A stress ECG should be performed on adults who have cardiovascular disease risk factors.

Medication that could influence airway response should be withheld prior to exercise: Methylxanthines and beta adrenergic drugs should be withheld for 8 hours; this is extended to 12 hours if long-acting preparations are taken. Anticholinergic drugs should not be taken for 8 hours before the exercise and 24 hours of abstention was suggested for sodium cromoglycate. Corticosteroids need not be excluded.

Prior to exercise, pulmonary function should be within 80% of the subject's usual baseline value and FEV1 should be at least 65% of the predicted value.

2.6 Equipment

A motor driven treadmill is most appropriate and exercise response should be monitored by ventilation rate or heart rate. If more careful physiological measurements are required, a cycle ergometer may be more appropriate.

2.7 Exercise procedure

The speed and gradient of the treadmill required to raise the heart rate to 90 % of predicted maximum was determined from a regression equation calculated by the authors (calculated from exercise test results for 35 subjects of varying age, size and fitness). Alternatively, an increase in oxygen consumption to 30-40 ml kg^{-1} min^{-1} was recommended. The following stepped approach was recommended but should be adjusted to the subject's observed response:

Table 1: GUIDELINES FOR STEPPED EXERCISE CHALLENGE (Eggleston et al, 1979)

STEP	DURATION	TARGET HEART RATE
I	2 min	50% predicted maximum
II	2 min	70% predicted maximum
III	5-8 min	90% predicted maximum

The target heart rate and oxygen consumption should be reached in 3-4 minutes and steady state exercise should be of 5-8 minutes duration.

Godfrey, Silverman and Anderson (1973) recommended that subjects exercise to a heart rate of 170 beats per minute (65-85% vO_2 max) for 6 minutes. All drugs except steroids were witheld for six hours prior to testing. This period is considered insufficient if current long-acting preparations are used. These authors

formulated an 'exercise lability' index :

$$\% \text{ rise in PEFR} = \frac{\text{highest PEFR during exercise - resting PEFR}}{\text{resting PEFR}}$$

$$\% \text{ fall in PEFR} = \frac{\text{resting PEFR - lowest PEFR after exercise}}{\text{resting PEFR}}$$

$$\text{Exercise Lability} = \% \text{ rise} + \% \text{ fall}$$

2.8 Assessing pulmonary function

Following earlier work (Jones et al, 1962; Jones et al, 1963), Jones (1966) advocated the standardised use of exercise and drugs to determine the asthmatic individual's 'bronchial lability'. Bronchoconstriction is determined by the fall in FEV1 after 5-8 minutes of free running and maximal bronchodilatation is determined after inhalation of aerosol isoprenaline followed by 1 minute of exercise. The use of this method of calculating the 'lability index'is not widely used.

Eggleston et al (1979) stressed that a representative baseline should be obtained before exercise testing. After exercise, measurements should be made at 1-2 minutes and then at 5-minute intervals until asthma subsides.

The most common way of expressing post-exercise pulmonary function has been to calculate the percentage fall from the pre-exercise baseline ie.

$$\% \text{ fall} = \frac{\text{Fall in FEV1}}{\text{baseline FEV1}} \times 100$$

The following is a summary of methods of expressing exercise response :

Table 2 : METHODS OF EXPRESSING POST-EXERCISE AIRWAYS RESPONSE

Measurement	Formula*
Maximum % fall	$100 \left(\frac{x - y}{x} \right)$
Maximum fall as % predicted	$100 \left(\frac{x - y}{p} \right)$
Lowest level as % predicted	$100 \left(\frac{y}{p} \right)$
Lowest level	y
Lability Index (Jones)	$100 \left(\frac{\text{FEV1 fall + FEV1 rise}}{\text{predicted normal FEV1}} \right)$
Exercise Lability (Godfrey)	PEFR % rise + PEFR % fall

* Note:
x = baseline function(eg.FEV1).
y = lowest function.
p = predicted normal value of pulmonary function.

2.9 Clinical applications

An obvious use for these testing procedures is to screen asthmatic subjects for participation in sporting activities, or work-related physical activity. The protection afforded by medication can also be assessed. It is also important to screen individuals who develop unexplained dyspnoea, cough or other respiratory complaints during exercise.

The investigation of EIA in controlled laboratory conditions is best determined using a treamill running protocol. However, selection of the mode of exercise is ultimately determined by the purpose of investigation. This is discussed more fully in section 2.3.

2. THE HISTORY OF THE DEVELOPMENT OF PHYSICAL TRAINING PROGRAMMES FOR ASTHMATIC PERSONS

James Livingstone of London (1935), was one of the first to publicise the value of breathing exercises in the treatment of asthma. Prior to this, breathing exercises had been more widely offered by persons outside the medical profession, for example in the 1920's, singing teachers had successfully treated many asthmatics. An early medical report of the therapeutic value of humming exercises was written by a Dr Hofbauer of Vienna in 1928.

After the second world war, publications on the subject resumed. Early investigators (Baker,1951; Livingstone, 1952; Dorinson, 1954) recognised the abnormal breathing pattern during asthmatic episodes and recommended therapy which included :

i) The re-education of automatic diaphragmatic movements to diminish thoracic-type breathing.

ii) Stabilisation of the chest wall to correct kyphosis.

iii) Deflation of lungs by increasing the expiratory phase of respiration.

Baker (1951) introduced exercises such as boxing and competitive games. Psychological damage as a result of the disease was thought to play a major role in the morbidity experienced by asthmatics (Livingstone, 1952) and relaxation exercises were added.

The first controlled study of the effects of exercise in the treatment of asthma was conducted by Fein, Cox, and Green (1953) on men who had been discharged from military service. Breathing exercises resulted in an improvement of chest movements that was greatest in the trial group, less in the home exercise group with

no change in a control group. No statistics were used, subject groups were small and many of the variables were uncontrolled. This type of study prevailed for many years.

Physical inactivity seemed to be the norm in the asthmatic population and concern was expressed by Scherr and Frankel (1958) that 'repeated suppression of physical exercise occurs in asthmatic children, a lifelong pattern may be set up which may prevent the patient participating in physical activities.' They developed an exercise programme which included games, boxing, wrestling, and judo and reported that almost all the subjects adjusted successfully to the activities of 'normal children'.

In 1958 Miller correctly criticised previous studies which had used statistical averages for random groups of patients with wide physiological variation. Training programmes were often of inadequate intensity, duration and supervision and were not standardized. Miller questioned the use of breathing exercises to train the diaphragm and quoted Wade (1954) : 'direct voluntary control of the diaphragm does not occur as a consequence of training. Rather, control of abdominal and lower thoracic muscles causes the diaphragm to move up, and the chest cage down.' Miller had a more holistic approach which included patient education, breathing exercises, and effective use of nebulised medication.

McElhenney and Petersen (1963) were the first to apply meaningful statistics to the results of a pilot study undertaken at the University of Texas. They found that a physical training programme produced a statistically significant improvement in vital capacity, a 30% decrease in the severity and number of asthmatic attacks and a decreased need for symptomatic medication. Flaws evident in the study are that no control group was

used, and that the growth of the children could have explained the increased vital capacity, which is in any event not an indicator of airways obstruction.

Millman et al (1965) evaluated the effect of a controlled exercise programme on asthmatic children and introduced more strenuous activity than previous investigators, without pushing any child 'beyond his tolerance'. After the four month trial, maximum breathing capacity and cardiovascular fitness improved objectively, but (baseline) FEV1 remained unchanged relative to predicted values. However, no control group was included in the study and no statistical analysis of data was performed.

Goldman et al (1966) noticed that children found breathing exercises boring, resulting in poor compliance. They introduced games to simulate breathing exercises, and callisthenics. Subjective improvement in clinical asthma was reported by most subjects and a small increase in vital capacity was noted. The authors advocated exercises such as: 'barking like a dog, sniffing, yelling, rope climbing, and balloon blowing'. The fun derived from such therapy probably contributed to the acceptance of this programme on an outpatient basis despite the subjective nature of the results of the study !

The first valid exercise study on the effect of an exercise programme on hospitalised asthmatic patients was conducted by Itkin and Nacman (1966). Exercises were conducted for two hours daily, five times a week. The crossover study design showed a statistically significant difference in vO_2 max between the control and post-training periods in both groups. VO_2 max was determined during a six-minute inclined treadmill run to exhaustion.

No change in resting FEV1 was noted during the trial. An observation concerning the evaluation of the long term effects of intermittent exercise was that many uncontrolled variables, such as the motivation and clinical condition of the patient, could introduce sources of error in the data.

The first study on the effect of a long term exercise programme on asthmatic children was conducted by Hyde and Swarts (1968). Lung function measurements (FEV1; vital capacity) did not improve after 3-8 months of the trial. This study has faults common with most of the studies of that period, namely there was no control group, no statistical analyses were performed and no consideration was taken of the growth of the children during the trial period.

Other studies of this period failed to show an improvement in cardiovascular fitness after short term (3 months - Chai et al, 1967) or long term (6 months - Vavra et al, 1971) training programmes, suggesting they were of too low an intensity.

Strick (1969) provided additional insights into the nature of exercise and asthma. He was aware of the general lack of evidence to support the concept of voluntary control of the diaphragm and saw the main aim of breathing exercises to improve ventilation, correct postural defects, and to increase the mobility of the thorax. He stated that it was unlikely that long term physical conditioning had any specific effect on the underlying disease processes but he felt that improved cardiovascular and neuromuscular efficiency allowed the same amount of work to be done with less effort. This theory still enjoys widespread support today. Strick recommended that asthmatic children should train with intermittent bouts of exercise, each of 1-2 minutes

duration.

Sly et al (1972) failed to demonstrate significant changes in pulmonary function at rest or in response to treadmill exercise after a twelve week training programme for asthmatics, who also showed no changes in personality as a result of the training programme. This well controlled study did however show a highly significant decrease in the frequency of wheezing during the three month trial period compared with an equivalent control period prior to the commencement of the training period. The importance of this result is lessened by the fact that the exercise group had significantly (threefold) more wheezy days prior to the trial period than did the control group.

A complete study of the haemodynamic responses to physical training requires invasive procedures. Vyas et al (1971) and Degre et al (1974) demonstrated an increase in vO_2 max after an exercise training programme in adults with chronic obstructive airways disease (COAD). The latter investigators also found an increase in maximal arteriovenous oxygen (a-v O_2) difference and a higher resting oxygen partial pressure after the training programme, which suggested an improved ventilation/perfusion ratio. There was considerable individual variation in respose to training amongst the patients, however.

Alpert et al (1974) reported a decreased post-training a-v O_2 difference (due to increased systemic mixed venous pO_2) during a submaximal cycle ergometer test despite an increase in cardiovascular fitness in five patients with COAD. It was thought that the increased 'muscular efficiency' resulted in decreased oxygen extraction from the circulation. The authors found that their

results were at variance with those of Paez et al (1964), Clausen and Trap (1970) and Larsen et al (1971). A possible reason for this result is that the patients had an abnormally high a-v O_2 difference at the onset of the study and that physical training tended to normalise that parameter. Alpert and colleagues failed to find a significant improvement in maximal voluntary ventilation (MVV) in response to the training programme, unlike an earlier study by Bass et al (1970) who showed this improvement. This result suggests that ventilatory muscle function can be improved after a training programme.

Adults with COAD were trained with daily treadmill walking by Chester and coworkers (1977). The specificity of the training resulted in a significant increase in the total work performed on the treadmill, despite the low intensity (mean heart rate was 125 beats per minute) of the training programme. There was also a decrease in O_2 consumption and minute ventilation during submaximal treadmill exercise after training; this was thought to be due to improved neuromuscular co-ordination and mechanical efficiency.

Swimming has been found to be the least asthmagenic exercise (Fitch and Morton, 1971; Anderson et al, 1975); thus Fitch and co-workers (1976) devised a training programme for asthmatics based on swimmimg. A noteable pre-requisite for entry into the programme was that subjects had to be able to swim 50m. Most of the 46 children had mild asthma and showed significant amelioration with puberty (classification taken from McNicol and Williams, 1973). Significant improvement in swimming performance was evident in the asthmatic group and in a non-asthmatic control group. The trained asthmatics required less medication and

clinical status improved after training. This could have have been due to seasonal or environmental pollen changes. EIA measured after treadmill testing was unchanged but this procedure was inappropriate as the subjects should have been tested with the exercise mode with which they had trained.

The Asthma and Allergy Institute in Voksentoppen, Norway was established in 1971, and has been involved in the research, diagnostic evaluation, treatment and rehabilitation of asthmatic children. In 1978 Oseid and Haaland reported that an exercise programme resulted in a 10-20% increase in aerobic capacity and considerable improvement in static and dynamic muscle strength in a group of ten asthmatic children. All children showed a decrease in heart rate in steady-state exercise on a cycle ergometer after training. The authors demonstrated an increase in $\dot{V}O_2$ max during treadmill exercise after two weeks of training. However, this could indicate familiarity with the apparatus, rather than improved aerobic capacity. No details were given about the workload or speed reached, nor the exercising respiratory exchange ratios of the subjects. There was also a decrease in post-exercise fall in PEFR in response to the same (individualised) submaximal ergometer test after the programme. The authors stressed that their findings did not necessarily mean that there had been any direct improvement in lung function. Rather, as a result of improved aerobic capacity there had been a smaller reduction PEFR in response to the same absolute exercise stimulus.

The 4-6 month exercise programme devised by these workers is comprehensive and seems more than that to which most (non-asthmatic) children have access. It included general endurance, strength and flexibility exercises, and an intensive two week

programme of skiing (winter), hiking, ball games, canoeing, kayaking (summer), and swimming (indoors). The authors noted that pre-medication with beta-adrenergic drugs or sodium cromoglycate was essential for successful training.

Graff-Lonnevig and colleagues presented work on the effect of a physical education programme on asthmatic boys at the ninth International Congress on Paediatric Work Physiology (Sweden, 1978). Training sessions lasted for one hour and was conducted bi-weekly for five months. Pulmonary and cardiovascular functions including blood volume, total haemoglobin, heart volume, total lung capacity, FEV1, functional residual capacity, residual volume and vO_2 max were unchanged after the training programme in the exercise group and in non-exercising control subjects.

It seems that the failure to show an increase in cardiovascular fitness can be attributed to the infrequent training sessions and the omission of pre-medication. The authors concluded that asthmatic boys can participate in a exercise training programme provided that modifications are made to the training schedule to avoid triggering EIA. The authors felt that pre-medication is necessary if the aim of training is to increase physical working capacity.

Keens (1979) published a comprehensive review of exercise programmes for paediatric patients with lung disease. He agreed with Faulkner (1968) who thought that exercise was limited by the capacity of the working muscles and the heart in normal persons, but that lung mechanics limited the exercise tolerance of patients with chronic lung disease. Keens postulated that improved of ventilatory muscle function might improve exercise tolerance.

This followed work by investigators who found that ventilatory muscle training improved exercise endurance in patients with COAD (Belman and Mittman, 1979 and in normal individuals (Leith and Bradley, 1976. The author cited a small number of studies which reported an increased aerobic capacity in patients with COAD after training (Christie, 1968; Degre et al, 1968; Nicholas et al, 1970; Mertens et al, 1970 ; Vyas et al, 1971). He concluded by recommending continuous aerobic activities for asthmatics, which he suggested should continue on a long term basis.

The effect of physical training on plasma citrate concentration in response to a bout of exercise in asthmatic children was investigated by Henriksen et al (1981). Asthmatic children were chosen because it was assumed that it was easy to demonstrate metabolic adaptation to training in that group of subjects. The trial group participated in a bi-weekly training programme for 6 weeks and the same treadmill testing protocol was used before and after the trial period. Plasma citrate levels were found to be significantly higher before and after the treadmill test at the end of the trial compared with the initial test. A corresponding decrease in plasma lactate concentration during the recovery period was reported. The results agreed with the authors' hypothesis that increased plasma citrate concentration (in muscle) may be of regulatory importance via inhibition of the key glycolytic enzyme, phosphofructokinase for the decreased lactate concentration following endurance training . No appreciable change in plasma free fatty acid concentration was noted as a result of training. A significantly smaller fall in PEFR in response to the same exercise bout was noted after the training period. This is at variance with previous reports and it is possible that the

small sample size (7) and the low intensity treadmill tests biased the results.

Another Australian study (Schnall et al, 1982) reported a successful training programme based on the previous swimming study of Fitch et al (1976) and their own work (Schnall and Landau, 1980). Three exercise groups were formed : One group performed 'dry land exercises' for 10 weeks, another group undertook a swimming training programme, and the third group did 5 weeks of each. The training which was on a bi-weekly basis resulted in improved cardiovascular fitness in all groups but there was no change in EIA or in clinical asthma for the duration of the study. It was concluded that asthmatic children could swim and participate in 'dry land exercises' resulting in minimal EIA if the activity was intermittent and if medication was taken.

A more strenuous exercise programme was devised by Bundgaard et al (1982). Sixteen adult asthmatics participated in a bi-weekly programme lasting for 2 months. Various intensive exercises lasting 30 sec were repeated on a circuit basis; a control group performed callisthenics and milder exercises- this probably corresponded with the maximal effort allowed in earlier studies. VO_2 max improved significantly by 10% in the exercise group whereas no significant change occurred in the control group. There was a 20% difference in vO_2 max between the sexes and this corresponds to the difference found in non-asthmatics. EIA in response to 6 minutes of free running was similar before and after the trial in both groups. The large number of dropouts (18) during the trial resulted in a homogenous group of highly motivated individuals. This study demonstrates that asthmatics can adapt normally to physical exercise and show the expected

improvement in vO_2 max.

In 1983 Nickerson et al reported that a 6 week distance running programme improved fitness without changes in EIA. The authors investigated the controversial 'optimal safe exercise prescription' for asthmatics. However, a number of faults detracted from the value of the study: the severity of the EIA may be questioned. In particular the fall in FEV1 at the onset of the study was <10% which does not fit the diagnosis of EIA; cycle ergometry was used as the stimulus for EIA; specificity of training resulted in an improvement in the 12-minute run (Cooper ,1968) but not in cycle ergometer performance which was therefore an inappropriate exercise testing mode for the study; and the authors assumed that the improved 12-minute run reflected an improved vO_2 max, but did not measure this directly.

The beneficial effects of exercise, whether subjective or objective shown by these studies, led to an increase in exercise programmes for asthmatics. By 1983 at least 70 such groups were active in Britain.

In Denmark, Henriksen and Neilsen (1983) compared the cardiopulmonary response to exercise before and after 6 weeks of endurance training. 28 asthmatic subjects were selected on the basis of their sedentary lifestyles and poor physical fitness levels. Improved aerobic fitness was confirmed by decreased maximal heart rate and post-exercise plasma lactate concentrations in response to a submaximal treadmill test. The post-exercise reduction in FEV1 was significantly reduced after the training programme but resting pulmonary function remained unchanged. The 14 asthmatic non-exercising controls did not show any change in the above parameters. The authors advocated premedication before

the training sessions, as recommended by Oseid and Haaland in 1978. Surprisingly, this was not standard practice despite its common sense, as most asthmatics restricted their exercise so that EIA did not develop. The significant reduction in the post exercise fall in PEFR probably reflects subject bias (sedentary individuals).

Arborelius and Svenonius (1984) agreed with Hartley's (1979) concept that EIA is a symptom of non-specific bronchial hyper-reactivity. The authors thought that the hyperpnoea that develops during exercise at intensities greater than the 'anaerobic or lactate threshold' is the stimulus for EIA. Their rationale for the reduction in EIA (after training) was that the 'anaerobic or lactate threshold' occurred at a higher workload, thus presenting a lesser stimulus for hyperpnoea. This theory did not explain all the findings in their study; in particular they did not measure ventilation and they suggested some putative mechanisms by which training may influence EIA. The three groups of children who trained with premedication (inhaled salbutamol; sodium cromoglycate or a combination of the two) showed significant improvement in cardiovascular fitness and a reduction in EIA.

Holzer et al (1984) investigated the effect of a home exercise programme for children with either asthma (37 subjects) or cystic fibrosis (41 subjects). The subjects were instructed to exercise for 30 minutes daily for three months ; matched controls were instructed not to exercise. The activities were based on the 5BX and XBX graded series of exercises developed by the Royal Canadian Air Force (1974). There was a significant improvement in the vO_2 max of the cystic fibrosis group only. Baseline lung

function tests remained essentially unchanged in all the groups but there was a significant improvement in maximal inspiratory pressure in both trial groups, probably due to a learning effect. An increase in maximal expiratory pressure was observed in the asthmatic trial group and this suggested an improvement in respiratory muscle function. An important feature of this study was that with time, both exercise groups reported diminishing compliance with the home exercises. This point, as well as the use of an inappropriate cycle ergometer test, contributed to the finding of a lack of a significant improvement in aerobic fitness. It can be concluded that home exercise programmes are of limited value for asthmatic children, as continued supervision and motivation seems essential.

Whitman et al (1985) built the concept of self-help into an exercise and educational programme. The following skills were taught: breathing control; body relaxation; bronchial hygiene; and physical conditioning. Anatomy and physiology lessons were also given and parents were included in the programmes. There was a significant decrease in the frequency of asthmatic episodes in preschool and scholar groups. Both control and trial groups showed a reduction in the number of days with asthma before and after the trial period. However, the important feature was that the patients' families were involved in the management of the asthmatic children and this increased the success of the programme, more than if the children had been left to their own initiative.

Orenstein et al (1985) conducted a well-controlled study of 20 children who participated in a tri-weekly four month running programme using beta-2 stimulants prior to each exercise session.

The training consisted of an initial warmup period, followed by a walking-running-walking phase at a speed sufficient to maintain the heart rate at between 70-85% of the maximal achieved during the initial maximal cycle ergometer test. Games were added and family and friends were encouraged to participate. VO_2 max increased significantly from 37.6 ml kg^{-1} min^{-1} to 43.1 ml kg^{-1} min^{-1} in the exercise group, but was unchanged in the control group. Of the pulmonary function variables, only MVV increased significantly in both groups. Clinical asthma judged by daily diary scores remained unchanged. EIA was not assessed in this study. At that stage, this study together with those by Itkin and Nacman (1966) and Bundgaard et al (1982) represented the few studies which show an improved vO_2 max after training in asthmatics.

A recent study by Ramazanoglu and Kraemer (1985) from Berne, Switzerland, investigated the cardiorespiratory response to physical conditioning in asthmatic children. Twenty three children completed an exercise programme (4.5 hours per week) which lasted for 15 weeks. No prophylactic medication was used and the exercise intensity was adjusted so that the exercising heart rates did not exceed 170 beats per minute. Significant improvement in baseline static lung volumes were found; in particular thoracic gas volume at functional residual capacity (TGV) and specific airway conductance (1/airway resistance/TGV) were both increased. There was also a significant improvement in vO_2 related to lean body mass in response to a submaximal cycle ergometer test (maximal heart rate 170-185 beats per minute). Mean working capacity during a comparative submaximal 6-minute cycle ergometer test (which led to a final heart rate of 170-185

beats per minute) also improved signficantly.

The authors used the following parameters to evaluate the cardiorespiratory response to exercise:

i) Breathing reserve (BR): the ratio between maximal achieved expired ventilation (VEmax) during a 6 minute 'endurance' test and the indirectly estimated maximal voluntary ventilation (MVV)

ie. (1-VEmax / Ind MVV)

Ind MVV = 35 x FEV1 (Indirectly calculated MVV at rest).

ii) Heart rate reserve (HRR) :

[1 - (HRmax-HRrest) / (HRmax predicted-HRrest)]

There were significant reductions in these parameters after the training programme. The authors hypothesized that lung hyperinflation is reversible with regular physical training with better use of cardiorespiratory reserves. The subjects were able to exercise at a higher percentage of their maximal cardiorespiratory capacity after training. However, only a small sample (14) were tested, no control group was investigated and seasonal factors may have influenced the results.

Summary

There have been relatively few studies showing an improved vO_2 max in asthmatic subjects after a physical training programme (Itkin and Nacman, 1966; Bundgaard et al, 1982; Orenstein et al, 1985; Ramazanoglu and Kraemer, 1985). In a study by Oseid and Haaland (1978), an increase in vO_2 max was observed after two weeks of physical training in asthmatic children. Insufficient data was given to determine whether this reflected improved aerobic capacity, or simply a learning phenomenon associated with

treadmill running. Other studies (Chai et al, 1967; Vavra et al, 1971; Graff-Lonnevig et al, 1978) failed to demonstrate this effect.

Some studies have shown an improved vO_2 max in patients with COAD (emphysema or chronic bronchitis or both with airways obstruction) in response to a training programme (Degre et al, 1974; Vyas et al, 1971). Similar studies showing improved aerobic capacity using other indicators include those by Christie (1968), Nicholas et al (1970) and Mertens, Shepard and Kavanagh (1978) who showed a decreased heart rate in response to submaximal exercise after a training programme. Chester et al (1977) also showed decreased submaximal oxygen consumption after a training programme.

These studies have also shown that improved cardiovascular fitness can only be achieved if pre-medication is taken so that the training can be of a sufficiently high intensity.

Many studies have investigated the effect of physical training on EIA. However, only a few have shown an objective improvement: Oseid and Haaland (1978) showed a lesser fall in PEFR in response to an exercise bout after a training programme; Henriksen and Neilsen (1983), and Arborelius and Svenonius (1984) demonstrated similar results using FEV1 as a measurement of airways obstruction. Recent studies by Orenstein et al (1985) and Ramazanoglu and Kraemer (1985) showed a decrease in lung hyperinflation after a training programme; the latter investigators also found improved resting specific airway conductance after a physical conditioning programme. All these studies demonstrated improvements in cardiovascular fitness, working capacity or muscle strength as

a result of the training programmes.

There have been numerous studies which did not show an improvement in EIA after a training programme. Important studies include those by Itkin and Nacman (1966), Hyde and Swarts (1968), Fitch et al (1976), Schnall et al (1982), Bundgaard et al (1982) and Nickerson et al (1983).

There have also been reports on the improvement of clinical asthma as a result of successful training programmes. Clinical improvement has been shown by decreased frequency of asthmatic attacks or lesser use of medication or both (McElhenny and Petersen, 1963; Sly, Harper and Rosselot, 1972; Bundgaard et al, 1982; Fitch et al, 1976).

Other investigators who monitored their subjects' clinical status found no improvement (Itkin and Nacman, 1966; Schnall et al, 1982; Nickerson et al, 1983; Orenstein et al, 1985). The conflicting reports can be reconciled if one considers the following points: small sample sizes and intra-group differences in the severity of EIA make comparisons difficult; some studies included children whose clinical asthma was improving (Fitch et al, 1976); diary scores rely on the reporting of subjective symptoms. It appears that in many asthmatics, clinical improvement is associated with increased physical fitness; however, it is difficult to associate the two as cause and effect. It is logical that an asthmatic person cannot effectively train if his or her clinical condition is suboptimal.

It is clear that the attitude towards physical training of asthmatic children has indeed changed since the first studies, many of which aimed to abort asthmatic attacks with breathing exer-

cises. The intensity of the training programmes has also increased remarkably over the years. Virtually any exercise can now be undertaken as long as pre-medication is given (sodium cromoglycate or beta-2 stimulants.)

Mild or moderate asthmatics should be able to train as effectively as non-asthmatics provided that their clinical asthma is controlled. It seems that education of asthmatics, their families, medical personnel and physical instructors remains the important obstacles preventing optimal management. The important stimulus has been the availability of formal training programmes, usually initiated by research centres or hospitals. This has been most successful in those studies undertaken in so-called First World countries. This approach is potentially successful and is needed in the Third World situation, but more basic health requirements remain priority over the limited financial resources available.

4. The initiating stimulus and EIA

4.1 Early work

It was initially assumed that expired air was at 37 °C and fully saturated. Webb (1951) devised a shielded thermocouple and demonstrated the air conditioning function of the nose: cold inspired air is warmed and expired air is cooled in the nose. Cole (1954) used thermistors to measure air temperatures between the nose and trachea during both quiet respiration and during hyperventilation. He concluded that the heating of inspired air occurs before the trachea while larger thermal burdens are conditioned more deeply in the respiratory tract.

Clinical observations indicated that cold weather exacerbated the frequency of asthmatic complaints. However, there was no formal research to substantiate this observation. A well controlled study by Wells and co-workers (1960) investigated the effects of cold air on respiratory airflow resistance in patients with obstructive airways disease. Pulmonary airflow was indirectly determined using an intra-oesophageal balloon technique. The authors speculated that the `normal processes of heating, humidification and filtration by the upper airways are altered or defective' in obstructive airways disease. This was later proved to be incorrect. They also speculated that the initiating stimulus for bronchospasm resulted from distal airway cooling or reflex mechanisms. It was also thought that increased viscosity of the respiratory mucosa could lead either to airway obstruction or to reduced heating of the inspired air.

Millar and colleagues (1965) extended the work of Wells and measured FEV1 before, during and after quiet breathing in a cold

room (-20 °C). Asthmatic subjects showed widely variable changes in FEV1 which were explained by differences in the sensitivity of a bronchial reflex. It was thought that the airway mucosa was cooled both directly and by the loss of latent heat of vapourization with progressive drying of respiratory secretions.

Caldwell et al (1969) recognised that the different protocols and equipment used to determine heat and water exchange during respiration made between-trial comparisons difficult. In an attempt to clarify some of the issues, the author used a complicated protocol to measure respiratory water loss at rest and during exercise. The authors concluded that the fraction of heat dissipated via the respiratory tract may be higher in patients with lung disease (chronic obstructive airways disease [COAD] and sarcoidosis) than in normal subjects. This result can be explained by the high ratio of ventilation to oxygen consumption during exercise in the diseased patients but does not necessarily prove that patients with COAD (or sarcoidosis) develop abnormal airway cooling during exercise.

4.2 The role of temperature and humidity of the inspired air

Strauss and co-workers (1977) showed that cold air and exercise could act synergistically in precipitating and sustaining EIA. Subjects performed exhaustive exercise on a cycle ergometer while breathing air at ambient and subfreezing temperatures. The authors hypothesized that stimulation of oropharyngeal receptors by cold air played a role in precipitating bronchospasm.

In a subsequent study Strauss et al (1978) found that humidity rather than temperature influenced lung function after exercise. The magnitude of airways obstruction was found to be inversely

proportional to the water content of the inspired air for temperatures from 25 °C to 37 °C. This appeared to be consistent with the idea that the quantity of heat transferred across the mucosal surface is a major determinant of susceptibility to EIA. An explanation is that the latent heat of vapourisation of water plays a quantitatively greater role in warming of the inspired air than does with direct heating (0.58 Kcal g^{-1} vs 0.304 cal $litre^{-1}$ $°C^{-1}$).

Bar-Or and co-workers (1977) referred to the following reports showing an effect of humidity on EIA :

i) Weinstein et al (1976) showed a benefical effect of ultrasonically nebulised normal saline delivered via an aerosol mask to asthmatics during running.

ii) Chen, Morton and Souhrad (1976) found that inspiration of warm humid air prevented EIA.

Bar-Or et al (1977) found that, at a constant ambient temperature, there was lesser bronchoconstriction after exercise undertaken in a humid climatic chamber compared to dry conditions. The authors compared this phenomenon to reduced EIA after swimming and agreed with suggestions by Chen and colleagues (1976) that the water and/or heat loss from the airway mucosa was a non-specific physiological stimulus for EIA.

4.3 The investigation of heat loss from the airways

Chen and Horton (1977, 1978) found that acute asthmatic attacks could be induced by cooling the body. It was hypothesized that body cooling led to airway cooling which triggered an asthmatic attack. In 1979 the authors supplied warm humid air to asthmatic subjects during exposure of the whole body to cold. Breathing

ambient room air with the body exposed to cold resulted in a significant decrease in FEV1. In contrast, in the majority of subjects, breathing warm humid air reduced but did not completely prevent bronchoconstriction induced by whole body cold exposure. The breathing of warm humidified air did not change the dose of methacholine required to produce a 20% fall in FEV1. Despite not having measured these parameters, the authors suggested that a lowered core temperature resulted in airway cooling.

In 1979, Chen, Weiser and Chai reported a study which was designed to determine whether EIA is primarily due to respiratory heat loss, respiratory water loss, or a combination of both. Asthmatic subjects were studied under four conditions of inspired air after the same treadmill walking protocol :

i) Cool dry air (CDA): 23 ^{o}C; 3 mg H_2O; 7.3 cal heat content l^{-1}.

ii) Oversaturated air (OSA): room temperature; 43 mg H_2O; 16.3 cal l^{-1}.

iii) Hot dry air (HDA): 120 ^{o}C;; 24.4 cal l^{-1} ; 3mg H_2O

iv) Warm humid air (WHA): 37 ^{o}C; 43mg H_2O; 34.7 cal l^{-1}.

Results showed a significant post-exercise fall in FEV1 after inhalation of CDA and OSA during exercise. Expectedly, inspiration of WHA and HDA did not cause a change in FEV1. The results showed that changes of post-exercise FEV1 and MMEF were caused solely by the heat factor and not by the water factor nor by an interaction of both. However it should be noted that two of five subjects showed bronchoconstriction after inhalation of HDA (10% and 12% fall in FEV1) and this is clearly at variance with the authors' hypothesis.

Deal et al (1979a) monitored retrotracheal (RTT) and retrocardiac

temeratures (RCT) during exercise and found similar falls following inhalation of cold air by asthmatic and non-asthmatic subjects. Polyethylene tubing was inserted into the oesophagus with 2 copper-constantin thermocouples attached to the tubing at 28 and 44 cm from the nares. These distances were chosen to represent retrotracheal and retrocardiac positions. The temperatures measured provide an indirect measure of temperatures in the respiratory tree; thus these results suggest that it is unlikely that asthmatics have a defect in the conditioning of inspired air. The asthmatic response was directly proportional to the absolute fall in RTT. This led to the hypothesis that the total heat flux in the tracheobronchial tree during exercise determined the degree of post-exertional airways obstruction in asthmatics.

This hypothesis was tested (Deal et al 1979b) by comparing respiratory responses to exercise in subjects who inhaled dry air at temperatures from subzero to 80 ^{o}C, to those that were predicted from a (theoretical) formula previously devised by the authors.

Respiratory heat exchange (RHE expressed as kcal min^{-1}) was computed from the following equation:

$$RHE = V_E [HC(Ti-Te) + H_V (Wi-We)]$$

where:

V_E : minute ventilation ($l\ min^{-1}$).

HC : heat capacity of air = specific heat x density = $0.304\ cal\ l^{-1}\ ^{o}C^{-1}$.

Ti : inspired air temperature (oC).

Te : expired air temperature (^{o}C).

H_v : latent heat of vapourisation of H_2O = $0.58\ kcal\ g^{-1}$.

Wi : water content of inspired air ($mg\ H_2O\ l^{-1}$ air).

We : water content of expired air ($mg\ H_2O\ l^{-1}$).

It was assumed that expired air was fully saturated at all Te.

EIA was observed at all inspired air temperatures, with the greatest falls in FEV1 occuring in response to inhaling air at $-10.9^{o}C$. Bronchoconstriction was attenuated, but not completely abolished with the addition of water vapour to inhaled air at $50^{o}C$. The authors to concluded that the total respiratory heat exchange played a role in development of EIA. The predicted and experimental relationship between inspired air temperatures and change in FEV1 were virtually identical for air from $-10^{o}C$ to $37^{o}C$. Greater calculated changes in FEV1 were observed for higher temperatures. This was explained by possible cooling of the hot inspired air in the mouth and pharynx.

The fact that EIA occurred at temperatures above $37^{o}C$ suggests that another factor (such as humidity of inspired air) may play a role in initiating bronchoconstriction. This was not discussed by the authors. Furthermore, the similar falls in FEV1 after exercise for inhaled air temperatures from $24.8^{o}C$ to $79.4^{o}C$ is not explained by their hypothesis of a directly proportional relationship between respiratory heat loss and the magnitude of post-exercise pulmonary changes.

Deal et al (1979c) have observed that the level of ventilation is an important determinant of the amount of heat transferred in the airways. It was reasoned that similar rates of ventilation would cause equivalent rates of heat exchange and corresponding degrees of airway obstruction. Eight young adult asthmatics performed isocapnoeic hyperventilation (ISH) at subfreezing and room temperatures (both dry), and with fully saturated air at room and body temperatures. During ISH, end-tidal pCO_2 is measured and CO_2

is added to the inspired air to maintain a constant pCO_2. Hyperventilation at body temperature did not result in a change in pulmonary mechanics. The bronchoconstrictor response was found to increase as the temperature and water content of the inspired air was decreased. The authors again concluded that the major stimulus for EIA was heat loss from the respiratory mucosa which was precipitated by the hyperpnoea of exercise rather than by exercise per se.

The above hypothesis appears to be at variance with earlier work (Deal et al, 1977) when the role of hyperpnoea was dismissed as a stimulus for EIA. In that study, exercise resulted in more airway obstruction than did isocapnic hyperventilation (ISH) for similar ventilation rates. However, no details were given about ambient temperatures or humidities which may have influenced the results. In a subsequent publication (1979c) the authors acknowledged that partial rebreathing of conditioned air occurred during the hyperventilation experiments and that this probably attenuated the subsequent bronchoconstriction.

4.4 Hydrogen ions and EIA

Deal cited several investigators who had documented a temporal relationship between increases in blood hydrogen ion concentrations with exercise and the development of subsequent bronchospasm. Vassallo and coworkers (1972) had proposed causality between these observations. The following is an explaination of the apparent association of changes in blood hydrogen ion levels and the heat flux hypothesis :

The rise in plasma lactate or hydrogen ion concentrations or both with exercise is accompanied by an increase in minute ventilation

disproportionate to the increase in oxygen consumption. The increase in ventilation is accompanied by an increase in respiratory heat loss, with subsequent development of bronchospasm as discussed above.

However, Strauss et al (1977) demonstrated that acidaemia was not the cause of EIA. Infusion of bicarbonate which prevented acidaemia developing during exercise did not attenuate the subsequent bronchospastic response.

4.5 Summary of the heat flux hypothesis

Deal and colleagues have contributed a substantial amount of knowledge concerning the initiating stimulus for EIA. Their unifying heat-flux hypothesis has subsequently become widely accepted. However, an important point is that the same eight subjects participated in the major studies which lead to the formulation of the hypothesis (1979a; 1979b; 1979c).

O'Cain and co-workers (1980) reported a study originating from the same Harvard medical school laboratories as the work by Deal. It was proposed that asthmatic subjects, rather than having a defect of air conditioning, are unusually sensitive to thermal burdens imposed on the respiratory tract. Non-atopic normal volunteers performed isocapnoeic hyperventilation (ISH) with cold dry air (CDA) and with air at body conditions. ISH at 123 l min^{-1} while breathing CDA resulted in significant alterations in partial expiratory flow volume curves (PEFV, done from 70% of vital capacity above residual volume). Identical ventilation rates while breathing saturated air at 37 ^{o}C did not alter PEFV. ISH with CDA at 61 l min^{-1} produced an intermediate fall in PEFV.

The authors therefore demonstrated that normal non-atopic subjects could respond to inhalation of CDA by developing measurable airways obstruction provided that the stimulus was sufficiently great. A small but statistically significant fall in FEV1 and MMEF was observed after ISH with CDA, but this was less than 10% of the baseline value (at 123 l min^{-1} !). It appears that healthy untrained subjects would be unable to reach rates of ventilation sufficient to demonstrate appreciable airways obstruction even when inhaling cold dry air.

4.6 Animal studies

Man et al (1979) studied the effect of temperature, relative humidity and mode of breathing on canine airway secretions. It was found that oral breathing resulted in an increase in osmolality of the airway secretions collected from the trachea. This led to the postulate that the hyperosmolality of airway secretions results from water loss from the airway mucosa during the conditioning of inspired air. A subsequent study on mongrel dogs (Boucher et al, 1981) confirmed the above findings. The transepithelial osmolar gradient (generated by evaporative water losses from the airway mucosa) was considered to be a driving force for hydration of the tracheal surface.

4.7 Respiratory water and heat losses

Ferrus et al (1980) quantified respiratory water losses during respiration at rest. Analysis of expired air was done with the aid of a mass spectrometer. It was found that the mass of H_2O lost per litre of ventilated gas is not a function of ventilation rate per se but increases as tidal volume rises and decreases as respiratory frequency diminishes.

Most previous studies examining the initiating stimulus for EIA had concentrated on the effect of inspired air temperatures. Investigators began to realise that the humidity of the inspired air was also an important factor. Re-examination of the results of previous investigators shows that EIA can occur after inhaling air at 37 ^{o}C or more. Chen et al (1977, 1978) appeared to concentrate their thoughts on the concept of respiratory heat loss, while others (Deal et al, 1979b) did not fully account for this observation.

Henriksen, Dahl and Lundqvist (1981) investigated how post exertional bronchoconstriction of different magnitudes influences the severity of airway response to a subsequent exercise test. It was found that breathing dry air increased, and humid air decreased the airways obstruction in response to exercise. This method was used to vary the initial degree of EIA in each pair of tests. Subsequent exercise tests an hour later (all at 50% relative humidity) resulted in similar degrees of bronchoconstriction irrespective of the initial degree of EIA. The authors interpreted this as evidence that mast cell derived mediators did not play a role in EIA.

Schoeffel, Anderson and Altounyan (1981) conducted the first study which investigated bronchial hyperreactivity in response to inhalation of ultrasonically nebulised solutions of saline of different concentrations. Airway response to the inhaled solutions was assessed by determining the rate of ventilation required to induce a fall in FEV1 of 20%. It had previously been shown (Allegra and Bianco, 1980) that asthmatics develop increased airways resistance after inhaling ultrasonically nebulised distilled water. This was confirmed by Schoeffel and

coworkers. Hypo- and hypertonic solutions of saline were found to be potent stimuli for bronchospasm compared with isotonic saline. These findings led to suggestions that :

i) lung irritant receptors may be stimulated directly by a change in osmolarity of the fluid lining the respiratory tract.

ii) change in osmotic pressure around mast cells may induce movement of water into or out of the cells. It had previously been shown that mast cells release histamine in response to hypotonic stimuli and that basophils release histamine in response to hypertonic stimuli. The released histamine may induce smooth muscle contraction either directly or reflexly via the vagus nerve.

Griffin, McFadden and Ingram (1982) re-examined the protective effects of nasal breathing on EIA. The results confirmed earlier work by Cole (1954) who showed that nasal breathing conditioned inspired air more completely than did oral breathing. Griffin and coworkers showed that the fall in RTT and RCT in response to nasal and oral breathing was similar in asthmatic and nonasthmatic subjects. The asthmatic subjects showed significantly greater airways obstruction after mouth breathing compared with nose breathing. Theoretically, nasal breathing will only be protective at relatively low levels of ventilation (various reports mention 30-60 l min^{-1} depending on inspired air conditions), above which rates oral breathing becomes essential.

McFadden and colleagues (1981) were aware of previous reports that the upper airways were unable to condition completely air at high ventilation rates. The severity of airway obstruction is apparently dependent on the magnitude of the temperature change

and the length of the cooled airways. In order to determine the site of final airway conditioning with the aid of a bronchoscope, the authors placed a thermocouple in a 6-7th generation bronchus of the anterior basilar segment of the right lower lobe . Progressively larger differences between inspired and expired air temperatures were observed with greater ventilation rates. It was also evident that the site at which inspired air reached body conditions varied with the rate and depth of inspiration. During quiet breathing air conditioning occurred in the upper airways. Inhalation of air at subzero temperatures resulted in the thermal boundary moving more to the periphery of the lung. An extreme example was illustrated with hyperventilation (60 l min^{-1}) with air at -17^{o}C : The mean inspired thermocouple temperature for 5 normal adults was 27.3^{o}C and the corresponding expired temperature was 32.3^{o}C. In contrast, a single inspired breath of room air was associated with a mean fall of 0.9^{o}C. With cold air (-17^{o}C) this manoeuvre resulted in a 2.5^{o}C fall. These results showed larger intra-thoracic temperature changes during respiration than was previously thought, and the role of temperature change as being the stimulus for EIA acquired new prominence.

Anderson et al (1982) investigated heat and water losses in asthmatic children who performed bicycle exercise while inspiring air at different temperature and water conditions. Rapid response thermistors were used to measure inspired and expired air temperatures and a mass spectrometer measured water vapour pressures. The authors found a large variation in bronchial response to the loss of heat and water from the respiratory tract during exercise. For the same fall in FEV1 the total heat and water loss

(corrected for body size) varied by a factor of 3. The subjects showed a greater sensitivity to heat loss. The water loss was related to the total ventilation and was greatest between the 5 th and 7 th minute of exercise. This was offered as a reason for the maximal degree of EIA occurring after 8 minutes of exercise (Silverman and Anderson, 1972). In half the patients, EIA occurred even when there was no significant respiratory heat or water loss. It was suggested that inhalation of hot wet air during exercise led to a gain in water by the airways. Their hypothesis was that a change in the osmolarity of the respiratory tract surface led to an increase in airways resistance.

An abstract published by Anderson et al (1983) reported on 17 asthmatic subjects who developed EIA after inhalation of hot dry air. The RTT did not change in adult controls and it was inferred that significant airway cooling had not occured. Anderson interpreted this as support for her hypothesis that a change in osmolarity of respiratory tract surface resulted in bronchospasm.

The effect of changing the osmolarity on the surface of the respiratory mucosa was investigated by inhaling solutions of different concentrations. Elwood, Hogg and Pare (1982) reported that the inhalation of hyper- and hypotonic saline solutions resulted in airways obstruction. They suggested that osmolar-induced cellular distortion leads to disruption of respiratory epithelium and irritant receptor stimulation, resulting in reflex bronchoconstriction.

Anderson, Schoeffel and Finney (1983) evaluated the use of ultrasonically nebulised solutions for provocation testing in asthmatics. The authors determined the delivered dose of inhalant required to induce a 20% fall in FEV1 and compared the fall in

FEV1 with equivalent doses of inhaled H_2O under different conditions. Results showed that there is a range of bronchial reactivity in response to the inhalation of distilled H_2O in asthmatics. This response was reproducible and in most subjects was independent of inhalant temperatures from 22 - 36 ^{o}C. It was subsequently suggested that documentation of individual reactivity and the change induced by medication could be of clinical importance. However, this technique may be another measure of non-specific bronchial hyperreactivity which can be assessed equally well using exercise, ISH or methacholine inhalation.

Another report (Higenbottam et al, 1983) compared the effects of a standard exercise test, ISH with cold air and with room air, and with ultrasonically nebulised distilled water in provoking EIA. Similar falls in FEV1 were observed for all four test methods in the asthmatic subjects; no change occurred in FEV1 in the controls in response to any of these stimuli. A direct relationship was found between the rate of H_2O loss from the airway and the fall in FEV1, suggesting that bronchial water flux may be the common factor explaining the production of asthma by all the methods described.

Ben-Dov, Bar-Yishay and Godfrey (1982) described EIA in an asthmatic boy who did not demonstrate respiratory heat loss. The extent of the EIA after inhaling cold dry air was the same as that after inhaling warm humid air. However, it is possible that the subject's response was related to his low baseline of FEV1 (53% of predicted normal).

A recent review (McFadden, 1983) discusses thoroughly the aspects of respiratory heat and water flux in the pathogenesis of

bronchoconstriction. Important points made by the author are :

i) Only 33-50% of the heat transferred to the inspired air is reclaimed during exhalation (Cole, 1953).

ii) The overall contribution of conductive and evaporative cooling to the total aiway temperature change is not known.

iii) It is possible that bronchial blood supply is reduced (via reflex bronchoconstriction) in response to cold stimuli in order to protect the core temperature.

iv) It is not known whether those with EIA have faulty regulation of the conditioning of inspired air, with defects in the recovery of heat and water, or whether they have abnormalities in bronchial circulation.

Eschenbacher, Boushey and Sheppard (1984) cited several authors who had shown that inhalation of nebulized solutions of low osmolarity and low ion concentration (distilled water) or high osmolarity and high ion concentration (hypertonic saline) cause cough and bronchoconstriction when inhaled by subjects with asthma, whereas iso-osmolar solutions (normal saline) rarely cause either response. Eschenbacher and co-workers were the first to examine ion concentration (of inhaled aerosols) as an independent variable in the pathogenesis of cough or bronchoconstriction. It was as yet unknown whether the stimulus for cough and bronchoconstriction from inhaled distilled water was its low osmolarity or low ion concentration. Adult subjects with mild asthma inhaled the following nebulized solutions :

i) hypo-osmolar without ions (distilled H_2O).

ii) iso-osmolar with ions (isotonic NaCl).

iii) iso-osmolar without ions (dextrose in H_2O).

iv) two hyperosmolar solutions.

Results showed that inhalation of isotonic aerosols with or without ions rarely caused bronchoconstriction. Significantly greater increases in specific airways resistance (SRaw) occurred after inhalation of hypo- and hypertonic solutions. It was also found that high ionic concentrations in hypertonic solutions acted as an additional bronchoconstrictor stimulus.

Low ionic concentration and hyperosmolarity appeared to be the stimuli for cough. Sodium gluconate (a large impermeate ion) caused cough, but rarely caused bronchoconstriction. These results suggested to the authors that different nervous pathways are involved for cough and bronchoconstriction.

An abstract published by Aitkin and Marini (1984) reported on ISH challenges with several air conditions. ISH with warm ($50^{o}C$) humid air and with warm dry air resulted in a significant increase in specific airways resistance in both asthmatic and normal subjects. Responses were of greater magnitude and were more prolonged in the asthmatic subjects. The results led to the suggestion that a change in osmolality of fluid in the respiratory mucosa may be the primary stimulus for bronchoconstriction.

Hahn, Anderson and coworkers (1984) continued investigation of the water-loss hypothesis. They re-evaluated the effect of temperature and the water content of inspired air on EIA. Ten asthmatic males undertook treadmill exercise at an intensity equivalent to 80% of their predetermined vO_2 max. The amount of heat (kCal) and water (ml) required to condition the inspired air was calculated assuming that the expired air was fully saturated. Significant falls in PEFR were observed after exercise with

inhalation of cold dry and hot dry air compared with inhalation of hot humid air. Compared to cold air inhalation, significantly less heat was required to condition the hot air whether it was dry or humid. Significantly less water was required to saturate hot humid air , and water loss was only half that required to condition dry air.

Calculations based on the conditioning of inspired air led to two potential sources of error :

i) No direct evidence exists that alveolar air is fully saturated and at 37 ^{o}C.

ii) No account was taken of the heat and water retained during expiration.

Data from different laboratories were compared graphically and two different regression lines revealed a variation in the correlation between severity of airways obstruction and water loss; the variation was greater for severity of airways obstruction vs heat loss. Because the airway response was similar for varied heat losses with constant water loss, it was concluded that water loss per se and not simply airway cooling is important in EIA.

An abstract by Smith and Anderson (1985) compared two asthmagenic challenge tests. The mean water loss required to induce a 20% fall in FEV1 (sensitivity) was calculated at 6.9 ml for ISH and 9.1 ml for inhalation of ultrasonically nebulised 4.5% saline. The slopes of the water loss/FEV1 response curves (reactivity) were compared in 11 patients who recorded >20% fall in FEV1 for each test. It was concluded that sensitivity and reactivity in response to water loss was similar for the two tests. The authors

interpreted this as support for the theory that airway hyperosmolarity may be an important mechanism for ISH-induced asthma.

A study by Eschenbacher and Sheppard (1983) re-examined the role of respiratory heat loss by having asthmatics perform stimulus-response curves (ventilation vs specific airway resistance) with increasing ventilation of (standardised) dry air. The purpose was to characterise accurately the bronchoconstrictory responses of each subject. Exhaled water content was also monitored.

In the first phase of the experiment RTT and RCT were measured during ISH at three temperatures of inhaled air (-8.4 ^{o}C, 20.5 ^{o}C, 39.4 ^{o}C). For each experiment, airway resistance (SRaw) and thoracic gas volume (TGV) was determined using a constant-volume, whole body plethysmograph. Baseline values were calculated from 5 measurements. Each subject then inhaled dry air through a mouthpiece at 20 l min^{-1} for 6 minutes while wearing a noseclip. The subject then returned to the plethysmograph for 5 more measurements of SRaw and TGV. If the SRaw had not doubled, the subject breathed dry air at 40 l min^{-1} for 6 minutes. In this fashion, each subject performed a stimulus-response curve breathing at 20, 40, 60 and 80 l min^{-1} if necessary. The experiment was stopped after the subject had developed a greater than 100% increase in SRaw over the baseline. The minute ventilation calculated to cause a 100% increase in SRaw was not significantly different for cold, room temperature, or hot dry air. The RTT fell more during inhalation of cold air, suggesting a greater degree of airway cooling, but this was independent of the ventilation rates required to cause an increase in SRaw by 100%. A thermocouple in the mouthpiece measured the exhaled temperature, but condensation of water vapour on the thermocouple

tip precluded accurate measurements of temperature and water content. The second part of the study used a novel apparatus in which the inspired and expired limbs of the respiratory apparatus were separate. The protocol was similar to the first phase. Exhaled water vapour was measured by weighing the tubing (of the expired limb) before and after each 6-minute period of ventilation. At temperatures of -21.4 °C and 38.9 °C no significant difference in ventilation was required to increase SRaw by 100%. As in phase 1, the minute ventilation required to cause a 100% increase in SRaw was not significantly different for cold or hot dry air. Using the values of inspired and exhaled air temperatures and inspired and exhaled water content, the respiratory heat loss and respiratory water loss was calculated at each ventilation for each subject. Stimulus-response curves were constructed using these values as the stimuli and the increasing SRaw values as the response; the (provocative) respiratory heat and (provocative) water loss that resulted in a 100% increase in SRaw over baseline were determined (PHL100 and PWL100 respectively). The authors found a significantly greater PHL100 for cold air when compared to hot dry air. Conversely PWL100 for cold air were significantly less than the PWL100 values for hot dry air. The authors concluded that neither the heat loss nor the water loss hypothesis could fully explain the bronchoconstriction induced by hyperpnoea with dry air in their subjects: they speculated that both may be stimuli for HIA.

Technical problems that arose were :

i) It was difficult to measure air temperatures with a single valve apparatus.

ii) Water vapour in the exhaled air condensed on the valve surfaces.

iii) The dead space of the valve allowed mixing of cool inspired and warm expired air.

iv) The chilled valve surfaces could act as a heat sink for exhaled air.

4.7 Summary of the Respiratory Heat Loss and Respiratory Water Loss hypotheses

The results indicate that neither respiratory heat loss nor respiratory water loss can fully explain the bronchoconstriction induced by ISH.

Early studies focused on the role of respiratory heat loss as being the stimulus for bronchoconstriction (Deal et al 1979a, b, c). Investigators found that bronchoconstriction still occurred despite minimal respiratory heat loss (Chen, Horton, 1977, 1978; Bar-Or, 1977; Anderson et al, 1983) and began to question whether RWL may also play a role in bronchoconstriction induced by hyperventilation. Anderson and co-workers investigated this concept extensively (1981, 1982, 1983, 1984) and showed convincingly that the humidity of the inspired air influences the degree of airways obstruction. However, this hypothesis does not explain all observations. A recent study by Eschenbacher and Sheppard (1985) demonstrates that both repiratory heat loss and respiratory water loss act as stimuli for bronchoconstriction. This appears to be logical and fits in with the concept that many non-specific

stimuli, for example exercise, atmospheric pollutants and ambient temperature influence airways obstruction in asthmatics.

An important point is that the authors used exercise and ISH as methods of inducing respiratory heat loss and respiratory water loss from the airways. Comparison of the above studies can only be made if one accepts that exercise and ISH represent similar stimuli for EIA.

Controversy exists concerning the acceptibility of the assumption that expired air is fully saturated. It has been shown that the initial volume of the expirate (from the upper airways) is 'dry' and the rest is fully saturated (Ferrus et al, 1980). The net result is that the exhaled air is slightly undersaturated.

Calculations assuming the above have overestimated the respiratory heat loss and respiratory water loss. The initial formula for calculation of RHL (Deal et al, 1979b) has been modified according to the protocol used and this makes inter-study comparisons more difficult.

The technique of thermistor measurement of inhaled air temperatures is not directly comparable between tests as the reading depends on the thermistor site and the surrounding structures (valve apparatus, airway mucosa).

It seems that quantification of respiratory heat loss and respiratory water loss will remain controversial until a standardised protocol is agreed upon. However, it is evident that both factors are responsible for initiation of EIA and ISH-induced asthma.

4.8 Irritant receptors

Observations by Schturman-Ellstein et al (1978) had given rise to the concept of temperature sensitive 'irritant-like' receptors in the posterior pharynx. It was thought that these receptors were esential in the pathogenesis of EIA.

McNally and co-workers (1979) anaesthetised the posterior pharynx of asthmatic children with lignocaine aerosol before treadmill exercise. A wide intersubject variation in the attenuation of EIA was found after lignocaine treatment. Saline aerosol administered to the pharynx offered no protection against EIA. This suggested that :

i) there may be temperature or humidity sensitive receptors elsewhere in the respiratory tract.

ii) the cool dry air used in the study possibly explained subject variability unrelated to the stimuli used by the investigators.

Enright, McNally and Souhrada (1979) reported significant protection against EIA with the lignocaine technique compared with saline. However, the significantly lower ventilation rate reached during the lignocaine study could have accounted for the results.

In a well controlled study Fanta, Ingram and McFadden (1980) failed to find evidence for irritant receptors. Similar degrees of hyperventilation-induced asthma were found after application of water and lignocaine to the posterior pharynx. Griffen, McFadden, Ingram and Pardee (1982) conducted a subsequent study using exhaustive exercise on a cycle ergometer. Pulmonary mechanics before, during and after exercise showed similar changes after administration of both saline and lignocaine.

Reports showing protection of asthmatic episodes by lignocaine can be criticised for their inadequate control. Well controlled studies using this technique have not revealed evidence for pharyngeal receptors responsible for the pathogenesis of broncho-constriction. The fact that such studies seem to have been discontinued indicates that investigators must now consider that irritant receptors to be an unlikely factor in EIA.

CHAPTER III

MATERIALS AND METHODS

1. SUBJECT SELECTION

Criteria for subject selection were determined largely by practical considerations : boys attending the Red Cross War Memorial Children's Hospital, Allergy Clinic who were aged 9-14 years, contactable by telephone, resident on a bus route to the hospital and who developed a fall in FEV1 greater than 15% after a standardised treadmill run (see section 2.4).

Letters were sent to the parents of prospective subjects whose details were obtained from folders at the Red Cross War Memorial Children's Hospital, Allergy Clinic by the Nursing Sister in charge. Ability to commute and contactibility of the subjects were the main factors which determined eligibility for entry into the study. All of the subjects were unknown to me at the beginning of the study. Twenty five subjects were willing to participate in the study and each subject and one parent were fully informed of the nature of the study. Signed consent was obtained from the parents before any testing began.

All testing was done at the Sport Science Centre (Medical School, Department of Physiology, UCT, Observatory). The screening resulted in exclusion of eleven volunteers for the following reasons: mild EIA (<15% fall in FEV1) on two separate days (8); gait problems from previous complicated meningitis (1); poor effort on the treadmill and misunderstanding of instructions (2).

Fourteen suitable subjects were divided into two groups of seven, forming the exercise and control groups. The two groups were initially matched according to the following criteria:

1) age

2) anthropometric measurements (height, weight, skinfold thickness)

3) vO_2 max.

I considered recruiting more subjects before starting the study but factors beyond my control intervened. For this reason I need to explain briefly the circumstances within which the study was conducted.

The Cape Flats was in political turmoil and it became dangerous to commute between Red Cross War Memorial Children's Hospital and the areas in which the subjects lived. Parents expressed anxiety about their childrens' safety especially if they had to rely on public transport. The boys whose parents felt it too unsafe to commute were allocated to the control group. This caused the groups to be unmatched in certain parameters as will be evident in the results (see results tables 3 and 4).

It was initially intended that both groups attend Red Cross War Memorial Children's Hospital simultaneously, with the control group watching video programmes whilst the exercise group trained. For the reasons described above, this was not possible and it was unavoidable that one group had more personal attention.

Twelve of the fourteen subjects completed the trial period with one drop-out from each group. One could not attend exercise sessions because of transport difficulties, and the other began a home exercise programme on his own initiative !

2. EXPERIMENTAL PROCEDURES

2.1 QUESTIONNAIRE

A questionnaire was sent to the parent(s) of the fourteen selected subjects. The questions enquired were the following: reasons for participating in the study; severity of the child's asthma; physical activity patterns of the child; attitudes of parent(s) towards physical fitness. Full details appear in Appendix I.

2.2 DAILY DIARIES

The format was modified from the diary cards which are used at the Red Cross War Memorial Children's Hospital Allergy Clinic. The workings of the diary were explained to the children. Fresh diaries were supplied monthly. (See Appendix V)

2.3. ANTHROPOMETRIC MEASUREMENTS

2.3.1. HEIGHT

Each subject was measured in bare feet with his heels, buttocks, back, and occiput flattened against a vertical wall. The vertical height was rounded off to the nearest centimeter.

2.3.2. WEIGHT

Body weights were measured using a Seca 770 Alpha Personal Scale (Vogel and Halke, Hamburg, FRG) with the subject dressed only in shorts. Figures were rounded off to the first decimal place.

2.3.3. SKINFOLD THICKNESS

This was measured in order to compute percentage body fat. A Holtain skinfold caliper (Holtain Ltd, Crosswell, Crymych, Dyfed, UK) was used to measure skinfold thickness at the following sites:

i) Biceps: over the mid-point of the muscle belly with the arm hanging loosely at the subject's side.

ii) Triceps: over the mid-point of the muscle belly mid-way between the olecranon and tip of the acromion, with the arm hanging as described above.

iii) Subscapular: immediately below the tip of the inferior angle of the scapula at approximately 45° to the vertical.

iv) Suprailiac: immediately above the iliac crest in the anterior axillary line.

Measurements were taken from the right side of the body in the standing position. The method was similar to that described by Durnin and Rahaman (1967), and computation was done using the calculation listed in Appendix III.

2.4. THE ASTHMAGENIC TREADMILL TEST

This was modified from studies by Silverman and Anderson (1972), and Eggleston (1979).

Subjects were required to refrain from all asthma medication for 12 hrs prior to the test (steroids excluded), and were not tested within a week of having recovered from a respiratory tract infection.

Three Medi-Trace pellet electrodes were adhered to the subject's anterior chest wall, and the ECG trace was displayed on a Life Trace monitor (Albury Instruments Ltd., London, England). The treadmill used was a Quinton air-cooled transformer type BA-1 (Tierney Electrical Motor Co., Seattle, USA).The ambient conditions were determined before the test began. Temperature varied from 21-26 °C, and relative humidity varied from 50-60 % (measured using a swing hygrometer (Casela, London, England).

All subjects ran with a model no. 2766 counterbalanced head support holding a model no. 2700 Rudolph valve (both by Hans Rudolph, Inc., Kansas City, USA). A nose clip prevented nasal breathing. Air was exhaled through clear-bore 35 mm tubing into a 15 l perspex mixing chamber with baffles. Ventilatory rates were determined from the inspired limb using a Morgan Ventilometer Mark 2 (P.K.Morgan Ltd., Gillingham, Kent, UK). The ventilation monitor was calibrated using a Collins chain-compensated gasometer (Collins Inc., Braintree, Mass., USA). The ventilation ($l\ min^{-1}$) and respiratory rate ($Breaths\ min^{-1}$) was recorded at the end of each minute.

The starting treadmill speed was chosen according to each subject's athletic ability. The speed was increased during the first two or three minutes until the heart rate reached 80% of the age predicted maximum. The subjects continued to run on the horizontal treadmill at the target speed for six more minutes, or until the subject voluntarily stopped because of EIA.

2.5. MEASUREMENT OF LUNG FUNCTION

Baseline lung function was measured before the treadmill test. PEFR was measured using a mini-Wright peak flow meter (Airmed, Clement Clarke International Ltd., London, England), and FEV 1, FVC, MMEF, were measured using a Type S Vitallograph spirometer (Buckingham, England). All subjects were well acquainted with these apparatuses. The highest value of three consecutive forced expirations was recorded throughout the test, and the best of two spirometer readings was recorded before the test began. Verbal encouragement was given for every expiratory manoeuvre.

The lung function tests which were performed before the treadmill test and were repeated at 2, 4, 6, 8, 10, 15, 20, 25 and 30 minutes after cessation of running. One FVC/FEV1 manoeuvre was measured at each time interval unless an obviously poor effort was noticed. Aerosol, or nebulised fenoterol was administered via a Hudson mask nebuliser using a pressurised O_2 source at 5-10 l min^{-1}, if the subject developed severe EIA. If the EIA was severe enough to prevent recording of FEV1 or FVC, these values were considered to be zero.

The same protocol was repeated at least two hours later. Fifteen minutes before the test, the subject inhaled two metered doses of fenoterol hydrobromide aerosol (2x200 mcg) (Berotec, Boehringer Ingelheim), and 20 mg of sodium cromoglycate powder (Lomudal, Fisons) 5 minutes before the test. The same measurements were made.

The asthmagenic test was done on all the subjects in March, July, and December (1985). The asthmagenic tests involving pre-medication was not done in March.

2.6 MAXIMAL OXYGEN CONSUMPTION

Maximal Oxygen uptake (vO_2 max) was measured using a continuous horizontal testing protocol[2].The subject had been acquainted with treadmill running on a prior occasion. Following a 2-3 minute warm-up run on the treadmill at 6 km hr^{-1} the test was started at 6 km hr^{-1} with speed increments of 0.5 km h^{-1} every 30 secs until voluntary exhaustion.

The same tubing, headgear, valves and noseclip decribed previously were used for this test.

Expired air from the mixing chamber was continuously sampled through Drierite anhydrous $CaSo_4$ (Vacumed Inc., Ventura, California, USA) to the sensors of an Ametek O_2 analyzer model S-3AI (Pittsburgh, Pennsylvania, and a Beckman LB-2 medical analyzer model 240M (Beckman Instruments Inc., Illinois., USA). The outputs of the analyzers were recorded on a Four Channel Chart Recorder model N 1-58-081 (Mennen Medical Ltd., Rehovot, Israel). The CO_2 analyzer for the final testing was an Amtek model CD-3A (Applied Electrochemistry, Ametek Inc., Thermox Instruments Division, Pittsburgh, PA., USA). Response times for both CO_2 analyzers were similar.

Both analyzers were calibrated before and after each test using either two or three gas samples of known concentration previously calibrated using the Haldane technique.

Ventilatory rates were determined from the inspired limb using the Morgan Ventilometer Mark 2.

Exercising heart rates were measured using three Medi-Trace pellet electrodes and recorded on a Life Trace monitor. The subjects' skin was prepared by initial abrasion with fine sandpaper. Dracard electrode gel (Dracard, Maidstone, Kent, UK) was applied to the centre of each electrode before attachment to the skin.

During the testing, heart rate, ventilation (l min^{-1}) and respiration rate (breaths min^{-1}) was recorded at the end of each minute. $F_E CO_2$ and $F_E O_2$ were recorded continuously on the chart recorder.

2.7. BLOOD LACTATE CONCENTRATIONS

Approximately two minutes before the start of the exercise test a 22G Jelco teflon intravenous catheter (Critikon, Tampa, Florida, USA) was inserted into a forearm vein. This was secured to 110 cm of polythene tubing (Internal diameter 0.86 cm, Portex Ltd., Kent, UK); this was in turn connected to 44.5 cm of plastic tubing ($0.80\ cm^3\ m^{-1}$) which was looped around the rollers of an Eyela Microtube Pump MP-3 (Tokyo Rikakikai Co., Tokyo, Japan). The speed of the pump was set so that sampling occurred 60 secs after the blood left the arm vein. Heparin was flushed through the tubing before the test to prevent blood clotting during sampling. During the exercise test, blood samples were collected every 60 secs and duration of sampling was 30 secs. Samples were also taken from the third to fifth consecutive minute after cessation of exercise.

Each blood sample was collected in plasic test tube which had been pre-weighed containing 2 ml ice-cold 2% perchloric acid (PCA). The deproteinized solution was thoroughly mixed by placing the tube against a Heidolph Whirimixer for approximately 5 seconds and stored in ice. The weight of the sampled blood was determined by subtracting the weight of the perchloric acid and tube from the total weight of the tube after sampling. On completion of the testing protocol, the deproteinized samples were spun in a refrigerated Beckman Centrifuge model TJ-6 (Galway, Ireland) for 10 minutes at 2000 rpm, the supernant was removed and was stored frozen for later analysis of lactate levels (see Appendix II).

The vO_2 max test, and the blood lactate determinations were performed on all the subjects before and after the exercise

programme (July and December, 1985).

3. DATA PROCESSING

3.1 Record keeping

An IBM-compatible CW-16 personal computer was used to store and manipulate raw data. The software programme 'Lotus 1-2-3', version 2 (Ashton Tate copyright 1985, USA) was used to store raw data, manipulate data, and to perform descriptive statistics.

3.2 Data interpretation

Apart from the data collected as described in the 'experimental procedures' section, the following data were selected to represent the respective measurements :

1) Height/weight/age: this variable was modified from Waterlow et al (1977) who suggested ways of presenting height and weight data for comparing nutritional status. These authors recommended a primary reliance on a) weight for height, as an indicator of present nutritional status, and b) height for age , as an indicator of past nutrition.

The anthropometric reference data representing 'healthy children' were adapted from NCHS data published by Ross Laboratories, Columbus, Ohio, USA (1976). These percentile graphs are routinely used at the Red Cross War Memorial Children's Hospital.

The method used was adapted to :

i) Find the theoretical age for the actual height of subject at the 50th percentile on the height/age growth chart.

ii) Locate the percentile on the weight/age growth chart from the

intersection of the theoretical age and the actual weight of the subject indicates the percentile.

This method utilises the height/age and weight/age charts, and eliminates use of actual age in predicting height or weight. The result is a weight for height estimation which differs from Waterlow's recommendations, which applies to children aged ten years or younger.

2) Ventilation during the last minute of an asthmagenic exercise test was selected to compare the response of the ventilatory system during submaximal exercise. This variable was generally highest during the last minute of exercise and was chosen in order to include the subjects who could not complete the test because of EIA, and those who completed 6-8 minutes of treadmill running. Comparison was made before, and after the training period in both groups, with and without medication. Ventilation during the last minute of the final test was compared with ventilation during the last minute of the initial test. However, if the subject ran for a longer period during the final testing session, the ventilation during the last minute of the first test was compared with the ventilation during the same time period in the final test. There was one exception where a subject ran for a longer duration during the first test; the ventilation during the last minute of the final test was compared with the ventilation during the corresponding minute of the initial test.

Duration of the asthmagenic treadmill test before and after the trial period was compared in all the subjects. This was done because several subjects developed EIA during the treadmill test, and could not complete the required 6-8 minute run.

iii) Blood lactate concentrations during the last minute of the initial maximal treadmill test were compared with the values for the corresponding minute during the final test. If a subject ran to a lesser maximum speed in the final test, the lactate concentration for the final minute was compared with the lactate concentration during the corresponding minute in the initial test.

Due to technical difficulties, final minute lactate samples were not obtained for two different subjects (two separate tests); in these two subjects, lactate concentrations during a common submaximal speed were compared.

Lactate concentrations during the last minute of the final test were also compared with the lactate concentrations during the last minute of the initial test (which was at a lower treadmill speed for most subjects).

4. STATISTICAL METHODS USED

4.1 Descriptive statistics

Mean, standard deviation, and standard error of the mean were computed for each variable using Lotus 1-2-3 and Statpak (Copyright 1983, Micropro International Corporation) software programmes.

4.2 Statistical tests

4.2.1. Paired t-test was used for within-group comparisons ie. before vs after the trial period.

4.2.2. Two-sample t-test was used to compare between-group differences before, and after the trial period.

4.2.3. Beta , or type II error was calculated assuming alpha (type I error) to be 5%.

4.2.4. N5% . As an aid to planning further studies an estimate was calculated of the number of subjects in each group, for each variable, that would be required for the difference between the two groups to reach statistical significance (p=5%). The calculations assume that the means and standard deviations would not change, and that both groups are normally distributed and are therefore optimistic in their predictions of the numbers required.

4.2.5. Confidence limits of the means was calculated for each variable (displayed graphically later).

The computer programmes for beta, n5%, confidence limits of the means was written by Dr M.Power of Medical Informatics, Groote Schuur hospital. The data were computed using Lotus 1-2-3, and Database III (Ashton Tate, copyright 1984). Listings of the programmes appear in Appendix III.

Statistical significance cut-off was set at p=0.05 for all variables.

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5. THE TRAINING SESSION

I initially approached the training sessions with a relaxed attitude in order to develop a rapport with the subjects.
The sessions consisted of :

1) warmup period
2) stretching exercises
3) callisthenics
4) breathing exercises
5) interval training
6) games

During the first few weeks more time was spent on less strenuous activities, with greater emphasis on interval training as the boys became fitter.

The training programme began early September, 1985 and ended on 28 November, 1985. A total of 23 sessions were held with one subject starting at session 7. A total of 116 sessions were attended out of a maximum of 132, representing an 88% attendance rate. Training sessions were held mostly on Tuesday and Thursday afternoons from 16H00 to 17H30. No training sessions were held during 2 separate weeks, mid-September and late-October, because of the withdrawal of bus services from the townships.

PEFR was recorded before the session began, and fenoterol aerosol was administered if a subject experienced wheeziness or if his lung function was subnormal. During the first few weeks of the programme PEFR was also measured during the session and additional aerosol was administered if necessary. This measurement was omitted as a routine and was only determined in those who developed an asthmatic episode, or in those who felt abnormally dyspnoeic. The subjects who developed bronchospasm were instruc-

ted to stop activity, to inhale two doses of fenoterol aerosol and to rest. They invariably returned to the session and would continue at a lower intensity until the symptoms resolved. PEFR was measured at the end of the session, and it was ensured that lung functions were optimal before the subjects were dismissed.

WARMUP

The warmup period involved walking and jogging slowly around the perimeter of the exercise area (±300m). The emphasis was on relaxation and the pace was regulated so that no-one became short of breath. This period lasted from five to ten minutes.

STRETCHING EXERCISES

These exercises were performed during and after the warmup period for a duration of approximately fifteen minutes. The subjects were instructed not to stretch till they felt pain and to hold a steady stretch rather than to 'bounce-stretch'. All stretches were held for 20-30 secs (unless otherwise stated). Each child progressed at his own rate over the weeks of training.

The following instructions were given :

1) QUADRICEPS STRETCH:

Kneel down with the toes pointed. Sit down so that each buttock rests on a foot. With legs slightly apart, lean backwards slowly until you feel your quadriceps stretch.

2) SITTING STRETCH FOR HAMSTRINGS AND QUADRICEPS of opposite leg: First sit with your right leg bent with your right heel next to you right hip. Keep your foot pointed straight back. Extend your left leg, keeping the knee flat. Hold your left ankle with

both hands and slowly draw your chin towards your left knee. Hold a position where tension is felt in the hamstrings. Repeat with opposite side.

3) GROIN STRETCH:

Sit upright with knees bent and soles together. Hold your toes and pull your feet towards your body. At the same time push down on your thighs with your elbows. Hold a position when you feel your groin muscles stretch.

4) GLUTEAL STRETCH:

Sit with your right leg extended in front of you. Bend your other knee and place your left foot to the outside of your right thigh. Hold your left knee with both hands and pull your knee to the right, keeping your foot flat on the ground. Repeat with other side.

5) CALF STRETCH:

Stand up slightly away from a wall and lean on the wall with both forearms. Flex your right leg in front of you with the foot flat on the ground. Extend your left leg behind you (with your foot flat on the ground), as far as comfort allows. Slowly move your hips forward keeping your lower back straight. Hold when a tight stretch in your calf is felt. Repeat with other leg.

6) ELONGATION STRETCH:

Lay flat on your back with toes pointed and arms extended over-head. Reach as far as possible in opposite directions with your arms and legs. Hold for five seconds and relax.

This stretch was repeated several times and was done after the strengthening exercises.

CALLISTHENICS

These were moderately intense exercises and were an extension of the warmup process. The following instructions were given:

1) WINDMILLS:

Stand up straight with your feet together and your hands by your sides. Jump up and and raise your arms sideways until they are above your head. Land with your feet about a shoulder's width apart. Jump up again bringing your legs together and your arms back against your sides. Do this 20 times, counting aloud !

2) LEG DRILL:

The starting position is similar to the crouch of a sprinter in the starting blocks, with the rear leg extended. The head is kept down while the legs rapidly alternate positions (forward/backward) while the hands remain as fixed support. Do this 20-30 times, counting every time a leg is extended backwards.

3) RUNNING ON THE SPOT:

Emphasis was placed on lifting the thighs until they were parallel to the ground. Short, rapid repetitions were practised.

STRENGTHENING EXERCISES

These were done after the callisthenics. We progressed slowly from ten repetitions of each initially to thirty repetitions at the end of the study. The following instructions were given:

1) PUSH-UPS:

Start by laying on your abdomen with hands parallel to each other and slightly more than a shoulder-width apart. Keeping your body rigid, raise yourself by extending your arms. Lower your body until your chest barely touches the ground, and push yourself up again.

2) SIT-UPS:

Lay on your back with your knees bent and your feet flat on the ground. Link fingers behind your head with your elbows touching the ground on either side. Begin by flexing your neck, then sitting straight up (trying to keep your feet on the ground). Lay down again slowly.

BREATHING EXERCISES

This was done after the callisthenics and at various times between the interval exercises. The aim was to make the subjects more aware of their breathing, and to have them utilise a full range of chest movement. The emphasis was on slow controlled breathing excursions, with an attempt to eliminate rapid shallow breathing.

The subjects were instructed to stand upright with their arms by their sides, exhale slowly until their lungs were 'empty', and inhale slowly until maximal capacity was reached. This exercise was repeated several times. Subjects were instructed to breathe initially through the mouth, thereafter through the nose until breathing became more relaxed.

INTERVAL TRAINING

No fixed order was followed and games were often included for variety. We however, invariably ended off with a game. These activities lasted from fifty to eighty minutes including rest periods.

Interval training included:

i) sprint drills : 50 - 100 m repetitions

ii) relay races

iii) hopping on one leg : 10 - 20 m

In hot weather we exercised in a swimming pool and this also included relay races and sprint drills.

Many games were tried and the following were more popular:

i) tag : an appropriately sized area would be demarcated; one person would be 'on'. His aim was to touch someone else who would then become 'on'. This game was quite tiring and could only be played for about ten minutes at high intensity. A variation was played with a tennis ball. One person would start off as being 'on'; hitting someone with the ball would also make him 'on'. The 'on' players were allowed to pass the ball to each other in their attempt to get everyone 'on'.

ii) hondjie : This is a variation of soccer where a small area is demarcated. Everyone is allowed to pass the ball except the 'hondjie' who has to try to get the ball from his opponents. The person from whom he manages to get the ball becomes the next 'hondjie'. This game developed soccer skills remarkably.

iii) soccer skills : many different variations were organised to develop soccer skills and sprint training simultaneously: short distance passing, ball control, and short runs with the soccer ball were practised for at least fifteen minutes.

iv) catching skills : this was introduced at the suggestion of one of the boys, and was played as a break between tiring activities. Two teams were formed and were approximately fifteen metres apart. Each person was given a name (eg.banana). A tennis ball was thrown high into the air, and an opponents' name would be called . He would have to catch the ball. We devised various scoring methods.

v) Swimming games : included polo, tag, ball catching.

vi) Soccer : proved to be the favourite, and the subjects regularly brought their soccer-playing friends. The teams were matched evenly, and games would last from forty to sixty minutes. If a subject developed bronchospasm during the match he would rest for several minutes after having two doses of fenoterol aerosol, then play goalkeeper until he was fully recovered.

CHAPTER IV

RESULTS

RESULTS

Measurements were made in March, July and December for most parameters, but discussion will focus on the latter two periods which correspond to 'before' and 'after' the trial period.

It was not possible to commence the training programme immediately after the July tests because of political turmoil which interfered with the daily lives of the subjects. The easiest option was to delay the training programme rather than have all the subjects return to the laboratory (in September) when it was least dangerous to commute.

On many occasions I gave the subjects lifts home after the training sessions. Roadblocks and the presence of Casspirs were a constant problem and this resulted in me having to vary the routes to the boys' homes. Considering the circumstances, it would have been impractical to have had more subjects than could fit into one vehicle.

On two separate occasions (mid-September and mid-October) public transport was stopped and access roads to some residential areas were sealed off by 'security forces'. Many children, including the exercise group were forced to remain at home for their safety.

I subsequently devised a home training programme for the exercise group in case they could not commute to the Red Cross War Memorial Children's Hospital (see Appendix IV).

Illustrations of intra-group changes in response to the trial period and 95% confidence limits of the mean changes are referred to in the text.

1.Anthropometric measurements

The anthropometric data for all subjects are presented in table 3.

TABLE 3 : MEAN ANTHROPOMETRIC VALUES FOR CONTROL AND EXERCISE GROUPS

		CONTROLS				EXERCISE GROUP			
		JULY	SEPT	DEC	DIFF D-J	JULY	SEPT	DEC	DIFF D-J
HEIGHT (cm)	MEAN	145	146	148	3 **	152	154	156	4 *
	SD	5	6	6	2	7	8	8	2
WEIGHT (kg)	MEAN	39.0	40.0	39.5	0.6	39.5	40.8	41.3	1.8 *
	SD	6.8	6.2	7.2	1.0	8.0	8.3	9.2	1.7
% FAT ~	MEAN		17.4	16.3	-1.1 **		14.4	13.6	-0.8 *
	SD		5.1	5.0	0.5		1.6	1.4	0.7

Note:
i) DIFF D-J : December-July differences.
ii) ~ = December-September values for this variable.
iii) Significant paired t-test p values: * $p < 0.05$
** $p < 0.005$

1.1.Height

The exercise group was significantly taller than the control group ($p=0.05$) at the beginning of the study, but the difference became less pronounced with subsequent measurements.

Both groups grew significantly taller during the year. For the 6 month period, the exercise group grew taller by a mean of 4 cm. and the control group grew by a mean of 3 cm. The difference in height increases is not significant.

1.2.Weight

The mean weights of the groups were similar despite the relatively large height and age differences (exercise group: 39.5 $\pm$ 8.0

kg.; control group: 39.0 ± 6.8 kg.) in July, implying that the control group was fatter than the exercise group. The average weight gain during the 6 month period was 1.8 kg in the exercise group and 0.6 kg in the control group. The difference between the improvements is not significant (p=0.15).

1.3.Percent body fat

The control group had a larger percentage body fat than the exercise group (17.4 ± 5.1 % vs 14.4 ± 1.6 %) when the subjects were measured in September. However, the difference is not significant (p=0.22). The final measurement was slightly lower in both groups and the decreases are statistically significant (exercise group: p=0.05; control group: p=0.004).

1.4. Height/weight/age

These data are presented in table 4. The anthropometric differences between the groups is reflected in this parameter. The mean centile of the control group is almost twice that of the exercise group (56.0 ± 24.3 vs 32.7 ± 18.8), but the difference is not statistically significant. This parameter remains relatively static for both groups during the year. The exercise group decreased by 2 centiles and the fall of 3.2 in the control group was found to be significant (p=0.05).

TABLE 4 : MEAN HEIGHT/WEIGHT/AGE VALUES FOR THE CONTROL AND EXERCISE GROUPS

CONTROLS	AGE (mo.)	JULY	DEC	DIFF D-J		EXERCISE GROUP AGE (mo.)	JULY	DEC	DIFF D-J
MEAN	140.2	56.0	52.8	-3.2	*	156.0	32.7	30.7	-2.0
SD	14.7	24.3	24.9	3.0		11.3	18.8	16.0	3.4

Note:
i) Ages are at the start of the trial period.
ii) DIFF D-J : December-July differences.
iii) Significant paired t-test p value: * $p < 0.05$

2.MEASURMENTS DURING MAXIMAL TREADMILL PERFORMANCE

2.1.Maximal treadmill speed reached (table 5)

The subjects in the trained group were able to run to a higher mean maximal speed in the post-training test (improvement of 1.25 ± 1.08 km h^{-1} ; $p=0.04$). No subject in the exercise group ran to a lesser maximal speed, while two subjects in the control group performed worse in the final test with only one subject improving on his maximal speed. The control group showed no mean improvement after the trial period. The difference between the mean changes is significant ($p=0.05$; figs 1 and 2).

2.2 Relative maximal oxygen consumption (table 5, fig 3)

The improvement in vO_2 max from 49.03 ± 5.03 ml kg^{-1} min^{-1} to 54.03 ± 5.22 ml kg^{-1} min^{-1} is highly significant in the exercise group ($p=0.01$). Five of the six subjects showed increased values after the training programme. The control group showed minimal change (0.85 ml kg^{-1} min^{-1}) which is not significant with only one subject showing an appreciable increase in relative maximal oxygen consumption. The improvement shown by the exercise group is significantly greater than that of the control group ($p=0.04$; fig. 4).

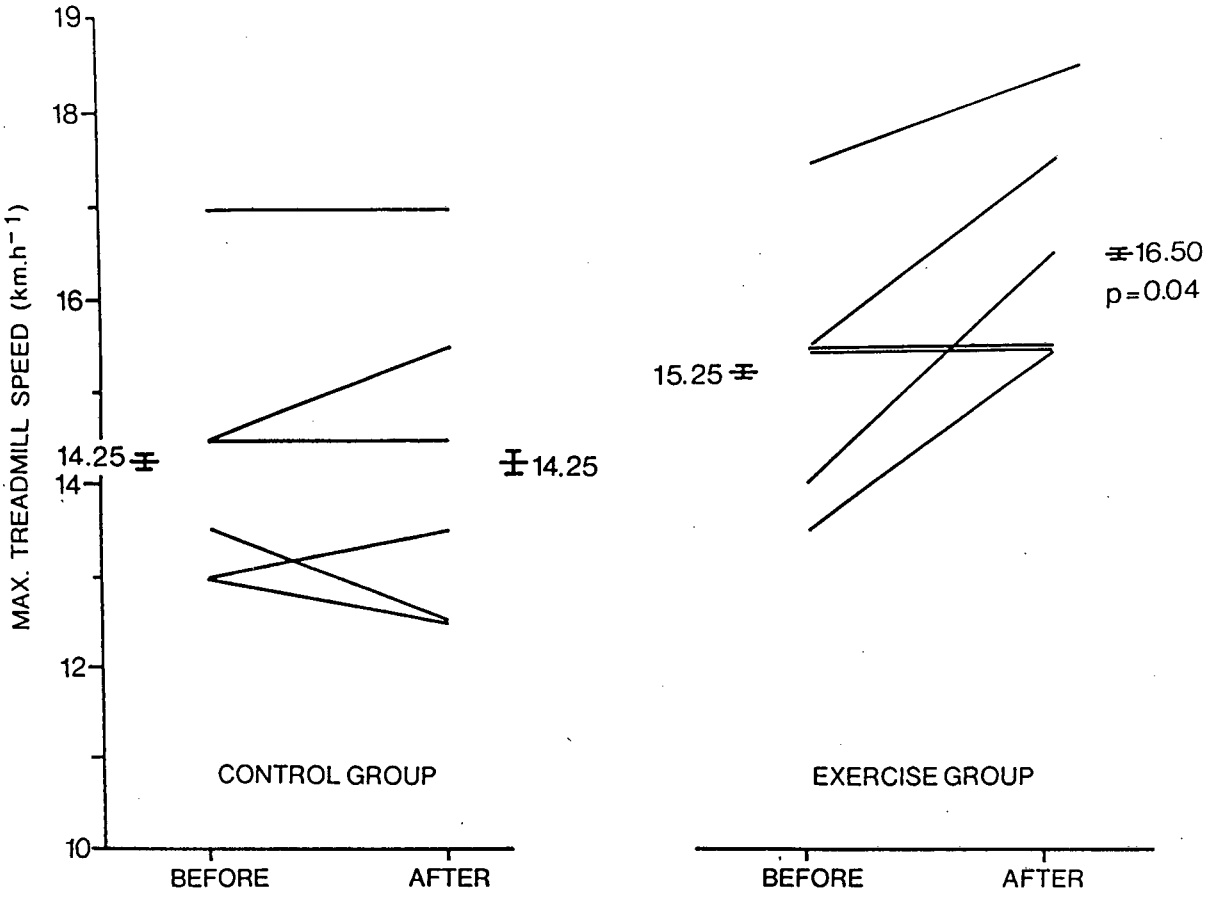


FIG 1: Individual results for maximal treadmill speeds reached during horizontal incremental treadmill testing before and after the trial period. Means, standard errors of the means (SE) and paired t-test p values are given.
n=6 for each group.

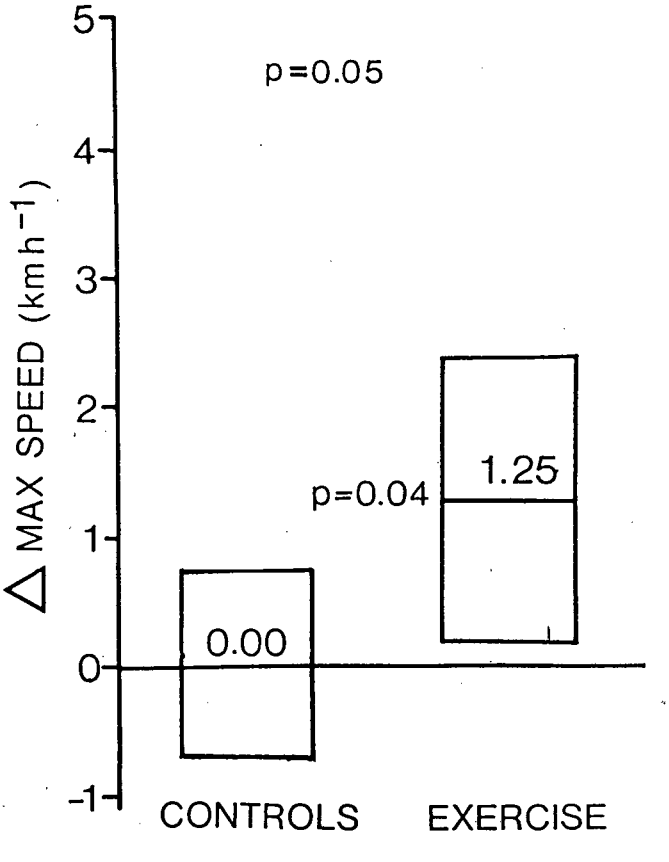


FIG 2: Mean improvements in maximal treadmill speeds with 95% confidence limits, p=0.05 for the two-sample t-test and p=0.04 for the paired t-test.
n=6 for each group.

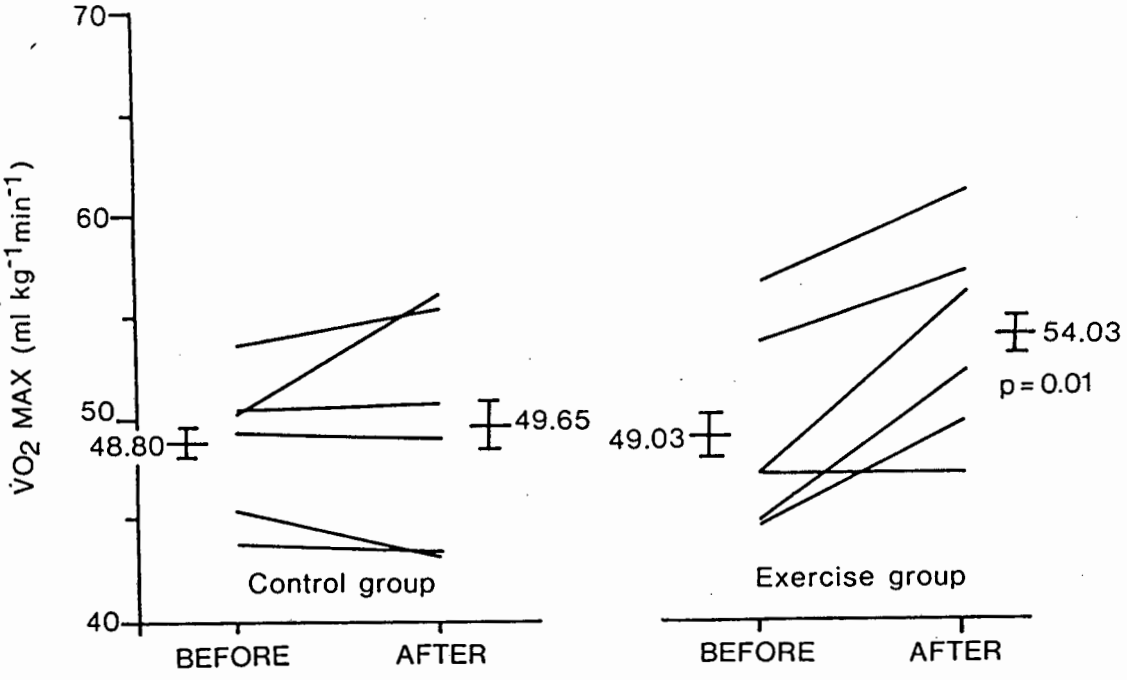


FIG 3: Individual results for relative maximal oxygen consumption before and after the trial period. Means, SE and paired t-test values are given. n=6 for each group.

FIG 4: Mean improvements in relative maximal oxygen consumption with 95% confidence limits. P=0.04 for the two sample t-test and p=0.01 for the paired t-test. n=6 for each group.

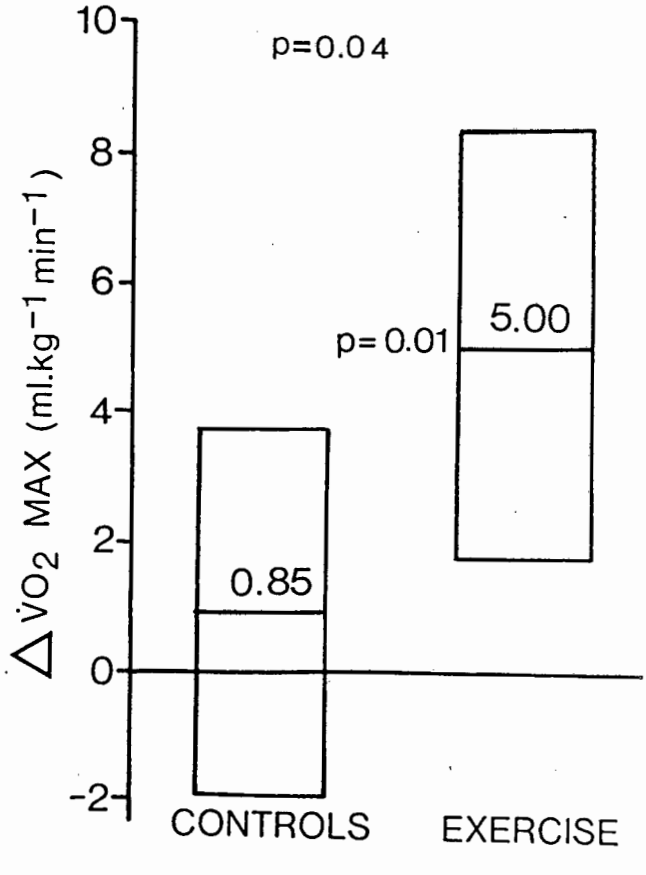


TABLE 5 : MEAN MAXIMAL OXYGEN CONSUMPTION (vO2max) AND MAXIMAL TREADMILL SPEEDS REACHED IN CONTROL AND EXERCISE GROUPS

		CONTROLS			EXERCISE GROUP		
		BEFORE	AFTER	DIFF	BEFORE	AFTER	DIFF
vO2max (ml/kg/min)	MEAN	48.80	49.65	0.85	49.03	54.03	5.00 *
	SD	3.66	5.66	2.83	5.03	5.22	3.24
MAX TREADMILL SPEED (km/h)	MEAN	14.25	14.25	0.00	15.25	16.50	1.25 *
	SD	1.44	1.78	0.84	1.41	1.26	1.08

Note:
Significant p values for paired and two sample t-tests: * $p < 0.05$

2.3.Absolute maximal oxygen consumption (table 6)

Almost all the subjects showed an improvement in this value, but the mean improvement in the exercise group (0.35 ± 0.16 l min^{-1} ; $p=0.003$) is significant whereas that of the control group (0.08 ± 0.10 l min^{-1} ; $p=0.12$) is not. The difference between the improvements is almost significant ($p=0.08$; figs 5 and 6).

TABLE 6 : MEAN ABSOLUTE VALUES OF MAXIMAL OXYGEN CONSUMPTION (vO2max) AND MAXIMAL CARBON DIOXIDE PRODUCTION (vCO2max) IN CONTROL AND EXERCISE GROUPS

		CONTROL GROUP			EXERCISE GROUP		
		INITIAL	FINAL	DIFF	INITIAL	FINAL	DIFF
vO2max (l/min)	MEAN	1.88	1.96	0.08	1.88	2.23	0.35 **
	SD	0.30	0.29	0.10	0.42	0.54	0.16
vCO2max (l/min)	MEAN	1.68	1.96 *	0.28	1.68	2.20	0.52 **
	SD	0.28	0.35	0.22	0.40	0.60	0.24

Note:
Significant paired t-test p values: * $p < 0.05$
** $p < 0.005$

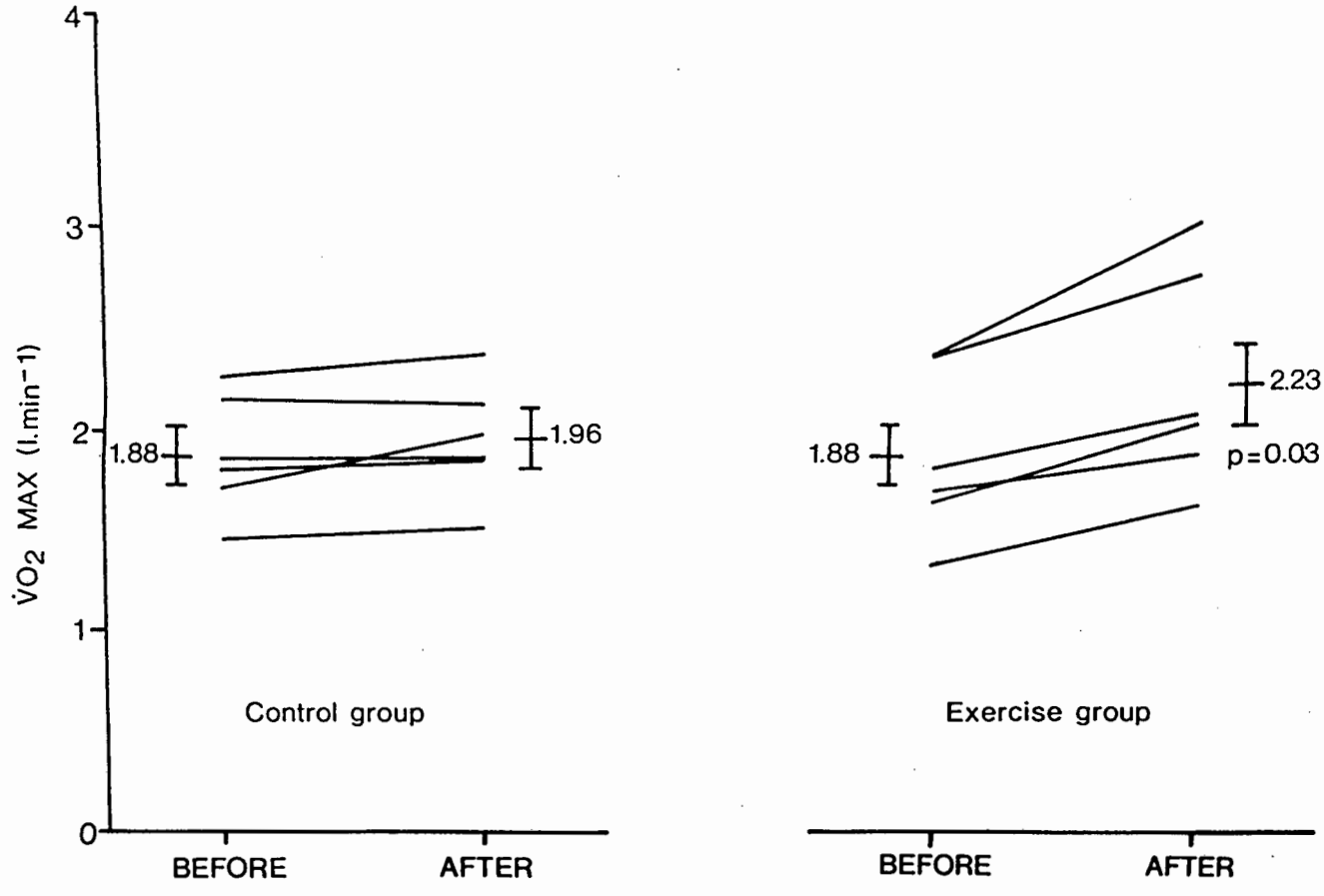
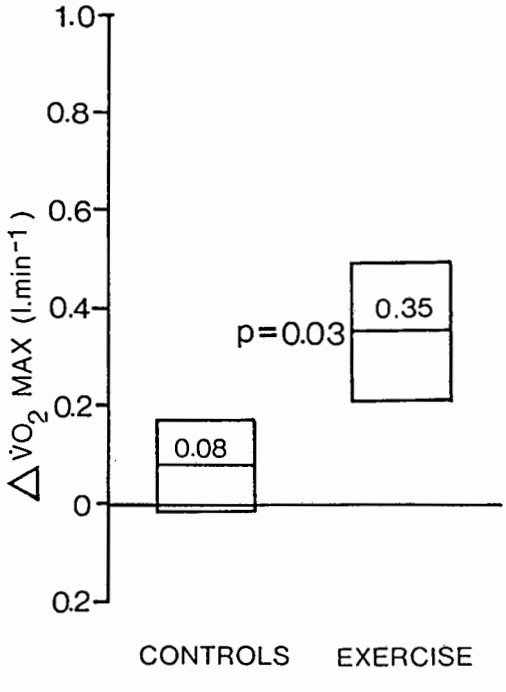


FIG 5: Individual results for absolute maximal oxygen consumption before and after the trial period. Means, SE and paired t-test values are given. n=6 for each group.

FIG 6: Mean improvements in absolute maximal oxygen consumption with 95% confidence limits. P=0.03 for the paired t-test. n=6 for each group.



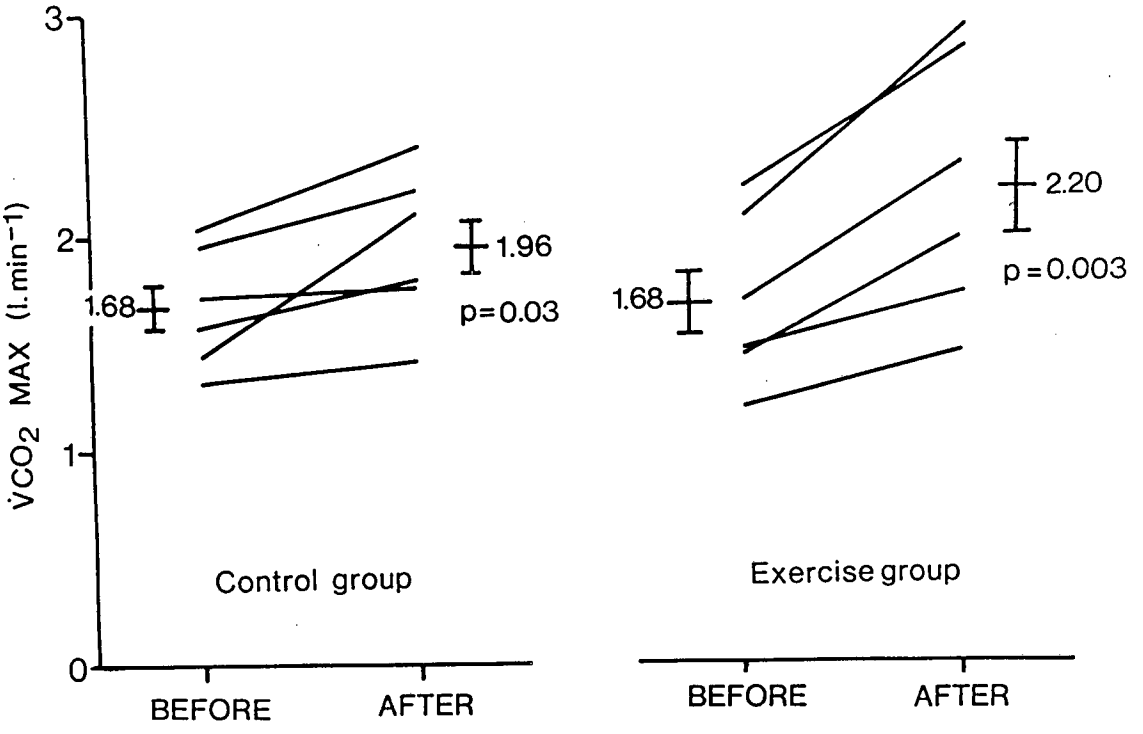
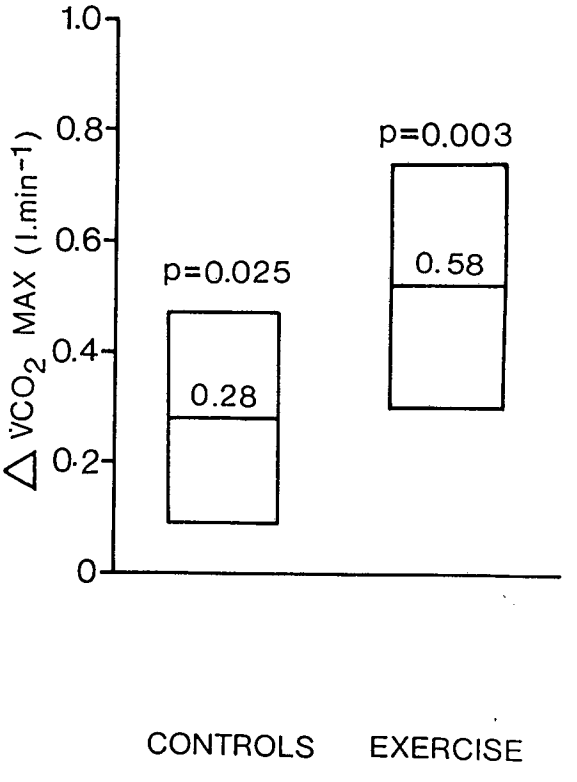


FIG 7: Individual results for absolute maximal carbon dioxide production before and after the trial period. Means, SE and paired t-test values are given. n=6 for each group.

FIG 8: Mean improvements in absolute maximal carbon dioxide production with 95% confidence limits. P values for the paired t test are given. n=6 for each group.



2.4.Absolute maximal carbon dioxide production (table 6)

This measurement mirrors the increase in absolute oxygen consumption and the improvements are statistically significant in both groups (exercise group: p=0.003; control group: p=0.025). The difference between the improvements is not significant (p=0.09; figs 9 and 10).

2.5.Respiratory exchange ratio at maximal oxygen consumption (table 7)

The respiratory exchange ratio (RER) is similar for both groups for the initial test (exercise group: 0.89; control group: 0.90) and both groups showed a greater ratio after the trial period (0.99 and 1.01 respectively). The improvement is statistically significant in the control group (p=0.01) and is almost significant in the exercise group (p=0.06).

TABLE 7 : MEAN RESPIRATORY EXCHANGE RATIOS AT MAXIMAL OXYGEN CONSUMPTION FOR CONTROL AND EXERCISE GROUPS

	CONTROL GROUP			EXERCISE GROUP		
	BEFORE	AFTER	DIFF	BEFORE	AFTER	DIFF
MEAN	0.90	1.01	0.11 *	0.89	0.99	0.10
SD	0.03	0.04	0.06	0.04	0.10	0.10

Note:
Significant p value for paired t-test: * $p < 0.05$

2.6.Blood lactate concentration (table 8)

The blood lactate concentration at the maximal speed of the initial treadmill test is compared to the blood lactate concentration for the corresponding speed during the final maximal test.

The blood lactate concentration did not show a consistent trend in the trained group and the final value was slightly lower than the initial value. The difference (0.06 mmol l^{-1}) is not significant (p=0.92). In the control group the mean value did not change significantly (0.64 mmol l^{-1}; p=0.14) and there is no appreciable difference between the intra-group changes.

TABLE 8 : MEAN BLOOD LACTATE CONCENTRATIONS ([LA], mmol/l) CORRESPONDING WITH THE MAXIMAL SPEED REACHED DURING THE INITIAL TREADMILL TEST FOR CONTROL AND EXERCISE GROUPS

	CONTROL GROUP			EXERCISE GROUP		
	BEFORE [LA]	AFTER [LA]	DIFF [LA]	BEFORE [LA]	AFTER [LA]	DIFF [LA]
MEAN	4.25	4.88	0.64	4.03	3.97	-0.06
SD	2.04	2.38	0.90	1.03	1.70	1.32

Note: DIFF [LA] : Differences in [LA] (after-before).

2.7.Blood lactate turnpoint (table 9)

The blood lactate concentrations were plotted against the running speed for each subject (two maximal tests each). The lactate turnpoint was determined by two methods:

i) The graph was visually inspected and the treadmill velocity just below the onset of lactate accumulation was recorded.

ii) The treadmill velocity that produced a blood lactate level of just below 2 mmol l^{-1} was used and this provided a more objective determination than the first method. A criterion of 2.5 mmol l^{-1} was used if a subject had a resting lactate concentration of greater than 2 mmol l^{-1}.

The value of 2 mmol l^{-1} has been used as an arbitrary value (Kindermann, Simon and Keul, 1979; Tanaka and Shindo, 1985). Six subjects (SA, NJ, NS, JB, BF, FI) had resting lactate concentrations of approximately 2 mmol l^{-1}.

TABLE 9 : LACTATE TURNPOINT 1 :
MEAN TREADMILL SPEEDS REPRESENTING THE MEAN LACTATE TURNPOINTS DETERMINED VISUALLY FROM BEFORE AND AFTER GRAPHS OF EACH SUBJECT

	CONTROL GROUP			EXERCISE GROUP		
	BEFORE	AFTER	DIFF	BEFORE	AFTER	DIFF
MEAN	9.17	9.33	0.17	10.67	12.33	1.67 *
SD	2.40	2.34	0.98	1.86	2.16	1.97

Note:
Significant p value for two sample t-test: * $p < 0.05$

LACTATE TURNPOINT 2 :
MEAN TREADMILL SPEEDS JUST BELOW BLOOD LACTATE CONCENTRATIONS OF 2.0 OR 2.5 mmol/l FOR THE CONTROL AND EXERCISE GROUPS

	CONTROL GROUP			EXERCISE GROUP		
	INITIAL	FINAL	DIFF	INITIAL	FINAL	DIFF
MEAN	9.50	8.67	-0.83	10.83	11.17	0.33
SD	1.76	2.07	0.98	1.17	2.40	1.97

Note:
Values in km/h.

No significant difference was found between the methods when the ordinary t-test and one-way analysis of variance was applied to the results. The exercise group showed an improvement in lactate turnpoint with both methods but this change was not statistically significant. The mean lactate turnpoint of the exercise group was however significantly higher than that of the control group after the trial period ($p=0.05$). However, minimal changes in lactate

turnpoint were found in response to training using both evaluation methods.

3.Measurements during the asthmagenic treadmill tests (table 10)

3.1.Treadmill run-time

3.1.1.Without premedication (table 10)

Three subjects in the exercise group and four in the control group were able to complete the prescribed eight minutes of treadmill running for the initial tests (March) after screening. A similar pattern was followed for the remaining tests and only two subjects in each group were able to complete the prescribed protocol on all three occasions.

There were no statistically significant differences between the inter-group run-times for each test period, or between the inter-group run-time differences.

TABLE 10 : COMPARISON OF DURATION OF ASTHMAGENIC TREADMILL TESTS, VENTILATION AND HEART RATES CORRESPONDING TO THE LAST MINUTE OF THE INITIAL TREADMILL TEST

		BEFORE			AFTER		
Without pre-medication:		Dur (mins)	Vi (l/min)	H.R. (B/min)	Dur (mins)	Vi (l/min)	H.R. (B/min)
CONTROL GROUP:	MEAN	6.17	45.85	179	6.33	47.67	186
	SD	1.60	4.61	16	2.07	10.68	11
EXERCISE GROUP:	MEAN	6.83	49.62	190	7.00	49.10	182*
	SD	1.83	10.42	6	1.26	9.68	7
With pre-medication:							
CONTROL GROUP:	MEAN	6.33	50.28	188	7.67 *	53.60	186
	SD	1.37	6.20	12	0.82	10.94	11
EXERCISE GROUP:	MEAN	7.50	52.13	193	7.67	56.32	189
	SD	1.22	13.11	11	0.82	9.47	6

Note:
i) Significant p value for paired t-test : * $p < 0.05$
ii) Dur : Duration of asthmagenic treadmill test.
ii) Vi : Inspired ventilation rate.

3.1.2.With premedication (table 10)

The run-time increased in the exercise group: the initial test was extended to a mean of 7.5 ± 1.22 minutes and the final test was extended to a mean of 7.67 ± 0.82minutes. A similar result was obtained for the control group: the initial test was marginally extended to a mean of 6.33 ± 1.37 minutes and the final test was extended to a mean of 7.67 ± 0.82 minutes.

The final run-time was significantly longer than the initial run-time in the control group ($p=0.04$).

3.2.Heart rate corresponding to the last minute of the initial treadmill test

3.2.1.Without premedication

The initial plan was to have compared the heart rates and ventilation rates during the last minutes of the eight-minute asthmagenic tests before and after the trial period. However, the inconsistent run-times made this impossible. In the majority of cases the December run-time was longer than the July run-time. It was decided that the best indication of cardiovascular fitness would be to compare heart rates and ventilation during the final minute of the initial (July) test with those measured during the corresponding minute of the final (December) test.

Exceptions were two subjects who ran for shorter periods during the final test: SA in the exercise group and SB in the control group. Heart rates and ventilation of these subjects during the last minute of the final test were compared to the corresponding minute in the July test.

The mean heart rate was significantly higher in the exercise group compared to the control group in the initial test (190 ± 6 beats min^{-1} vs 179 ± 16 beats min^{-1} ; p=0.04) despite similar run-times (mean difference of 0.67 minutes; p=0.52). The final mean heart rate was significantly lower in the exercise group (182 ± 7 beats min^{-1} ; p=0.02) and increased slightly in the control group after the trial period (186 ± 11 beats min^{-1}). The difference between the intra-group changes (15 ± 8 beats min^{-1}) and was not significant (p=0.09).

3.2.2.With premedication (table 10)

The mean heart rate was slightly higher compared to the non-premedicated test in both groups for both tests and there were no significant changes after the trial period.

3.3.Ventilation corresponding to the last minute of the initial treadmill test

3.3.1.Without premedication

The ventilation rates were similar for both groups (49.6 ± 10.4 l min^{-1} vs 45.85 ± 4.61 l min^{-1}) and no significant changes occurred in these values after the trial period (49.1 ± 9.7 l min^{-1} vs 47.7 ± 10.7 l min^{-1}).

3.3.2.With premedication

The ventilation rates were raised for all tests after premedication. The exercise group had a mean initial ventilation rate of 52.1 ± 13.1 l min^{-1} and a final value of 53.6 ± 3 l min^{-1} . The control group had values of 50.28 ± 6.2 l min^{-1} and 53.6 ± 10.9 l min^{-1} for these tests respectively. The differences between intra-group changes after the trial period was not

statistically significant.

However, the use of premedication significantly increased the ventilation rates in the control group for the initial and final tests: initial test : 45.9 l min^{-1} to 50.3 l min^{-1}, p=0.01; final test: 47.7 l min^{-1} to 53.6 l min^{-1}, p=0.03.

Similar increases in ventilation also occurred in the exercise group but this was not statistically significant.

A summary of mean changes (after-before) in parameters measuring fitness is presented in tabular form (table 11).

TABLE 11 : MEAN CHANGES (AFTER-BEFORE) IN PARAMETERS MEASURING FITNESS IN CONTROL AND EXERCISE GROUPS

CONTROL GROUP

	vO2max (ml/kg/min)	vO2max (l/mi	RER	Tmax (km/h)	LacTpt (km/h)	[La]MSi (mmol/l)	HR submax (B/min)
MEAN	0.9	0.1	0.1	0.0	0.2	0.6	6.7
SD	2.8	0.1	0.1	0.8	1.0	0.9	15.3
Prd t (p)	0.49	0.12	0.01	1.00	0.70	0.14	0.14

EXERCISE GROUP

	vO2max (ml/kg/min)	vO2max (l/min)	RER	Tmax (km/h)	LacTpt (km/h)	[La]MSi (mmol/l)	HR submax (B/min)
MEAN	5.0	0.3	0.1	1.3	1.7	-0.1	-8.2
SD	3.2	0.2	0.1	1.1	2.0	1.3	11.0
Prd t (p)	0.01	0.003	0.06	0.04	0.09	0.92	0.02

Comparison of intra-group changes using the two sample t-test :

	vO2max (ml/kg/min)	vO2max (l/min)	RER	Tmax (km/h)	LacTpt (km/h)	[La]MSi (mmol/l)	HR submax (B/min)
p value	0.04	0.08	0.92	0.05	0.14	0.32	0.09

Notes on table 11:

i)	vO2max:	Maximal oxygen consumption.
ii)	RER:	Respiratory exchange ratio.
iii)	Tmax:	Maximal treadmill speed reached.
iv)	LacTpt:	Mean lactate turnpoint determined visually from graphs of each subject.
v)	[LA]MSi:	Blood lactate concentration corresponding to maximal speed reached during initial maximal treadmill test.
vi)	HR submax:	Submaximal heart rate corresponding to the last minute of the initial asthmagenic treadmill test.
vii)	Prd t:	Paired t-test.

4.Lung function tests

Lung function response to exercise after premedication are not discussed as minimal perturbations were noted.

Discussion of mean values are not meaningful because not all subjects ran for the same duration and the run-times differed before and after the trial period. The individual results of one subject are presented with this in mind.

A typical response of FEV1, MMEF and FVC to an exercise bout is illustrated. Subject LA shows three different responses:

Fig 9: No inhaled medication was taken for 8 hours before the test. The FEV1 fell to 68% of the pre-exercise value and this meets the criterion for EIA. The MMEF shows a characteristically greater fall (57%) indicating small airways obstruction. The FVC is essentially unchanged (9% fall). Maximal airways obstruction is evident 6 minutes after the end of exercise with spontaneous reversal by 30 minutes.

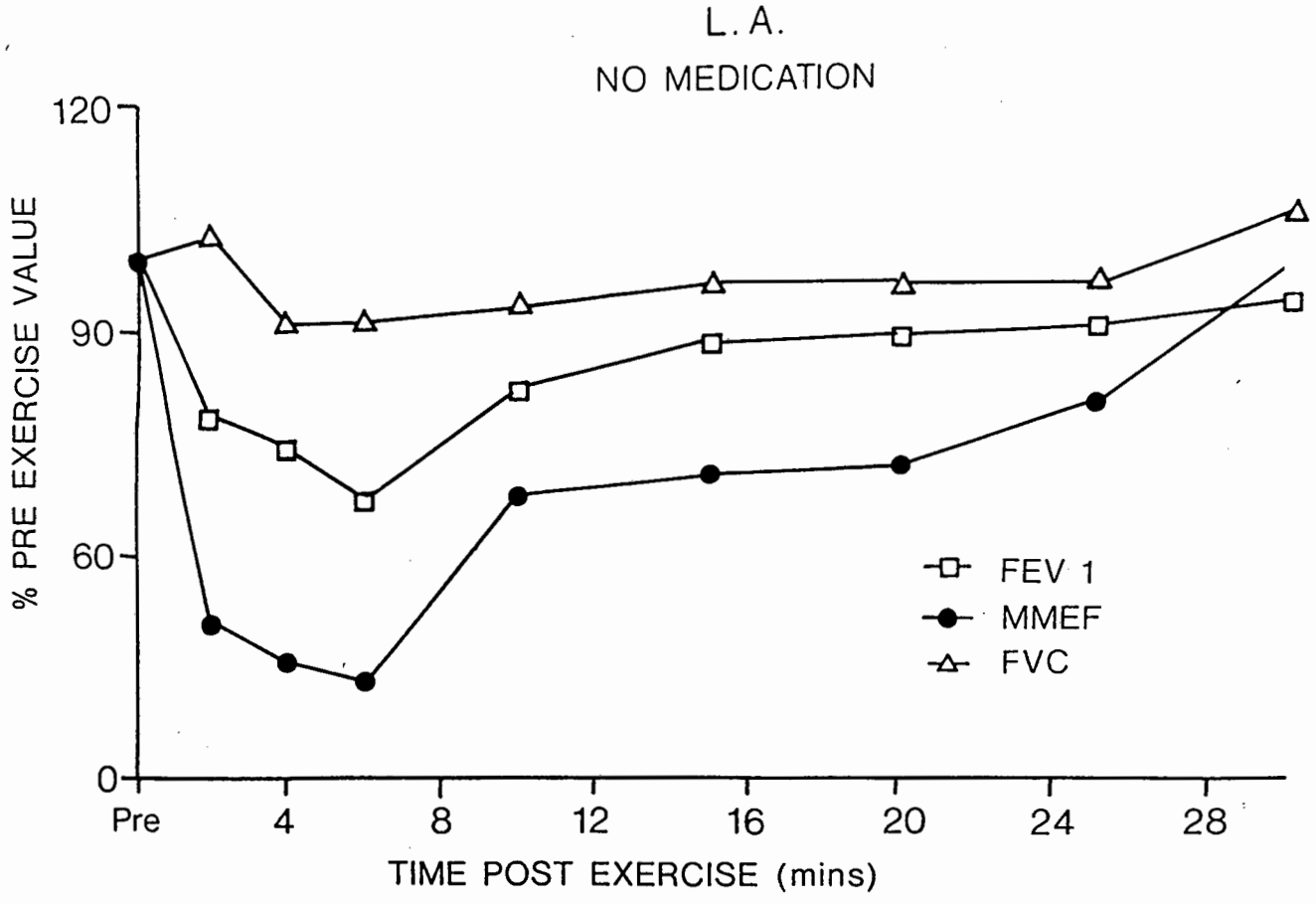


FIG 9: Characteristic post-exercise airways response without pre-medication demonstrated by subject LA.

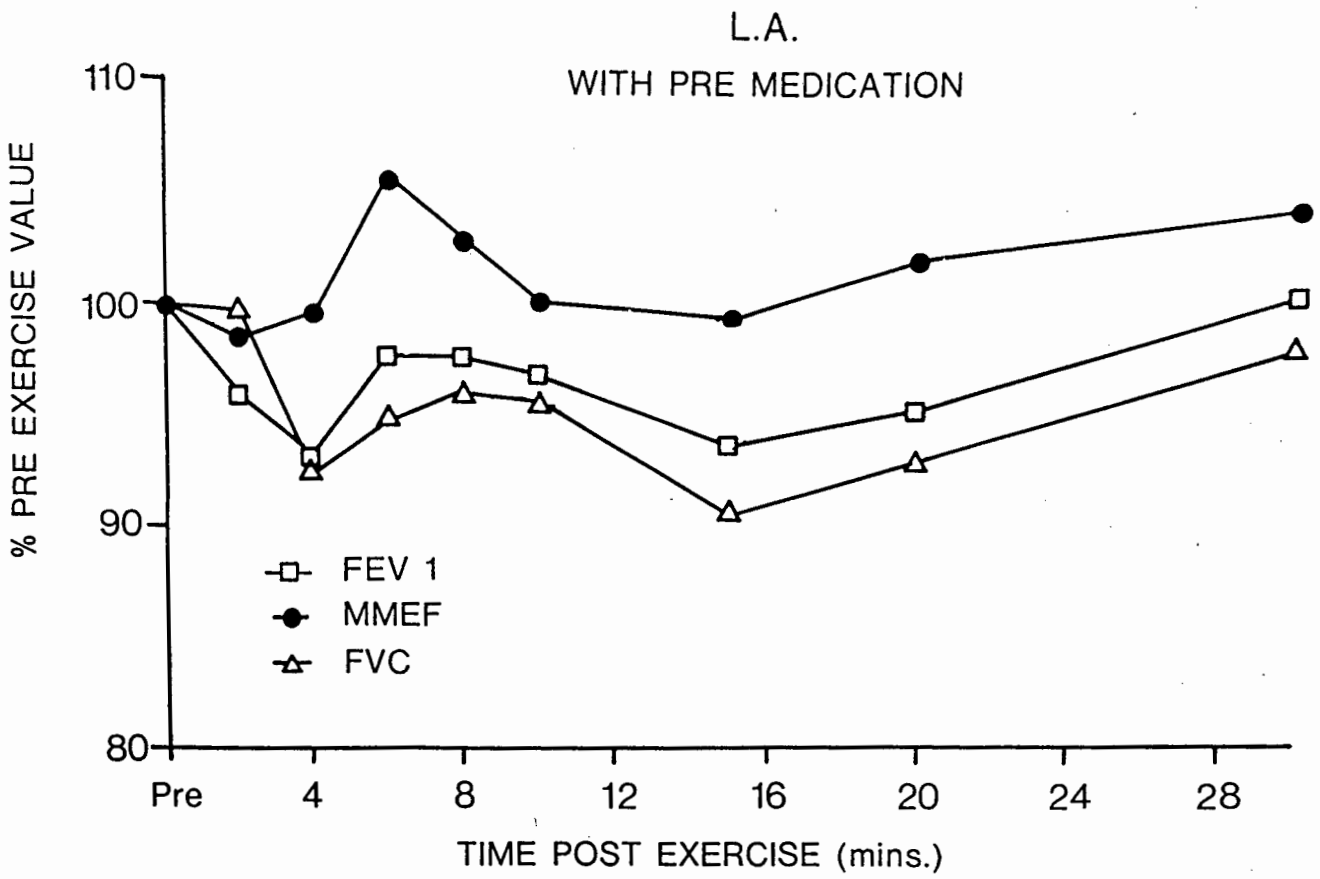


FIG 10: Attenuation of post-exercise airways obstruction with the use of pre-medication in subject LA.

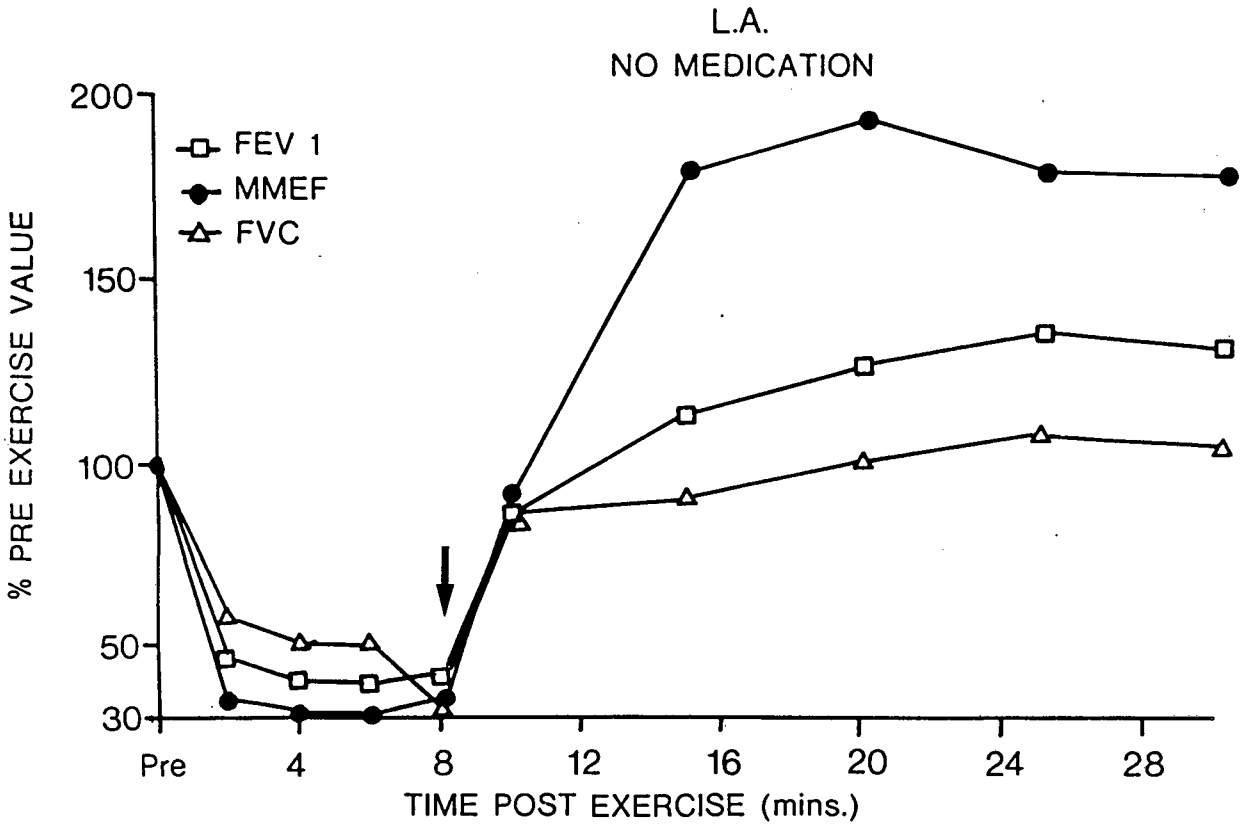


FIG 11: Severe post-exercise airways obstruction without the use of pre-medication in subject LA. Arrow indicates administration of nebulised fenoterol hydrobromide (Berotec).

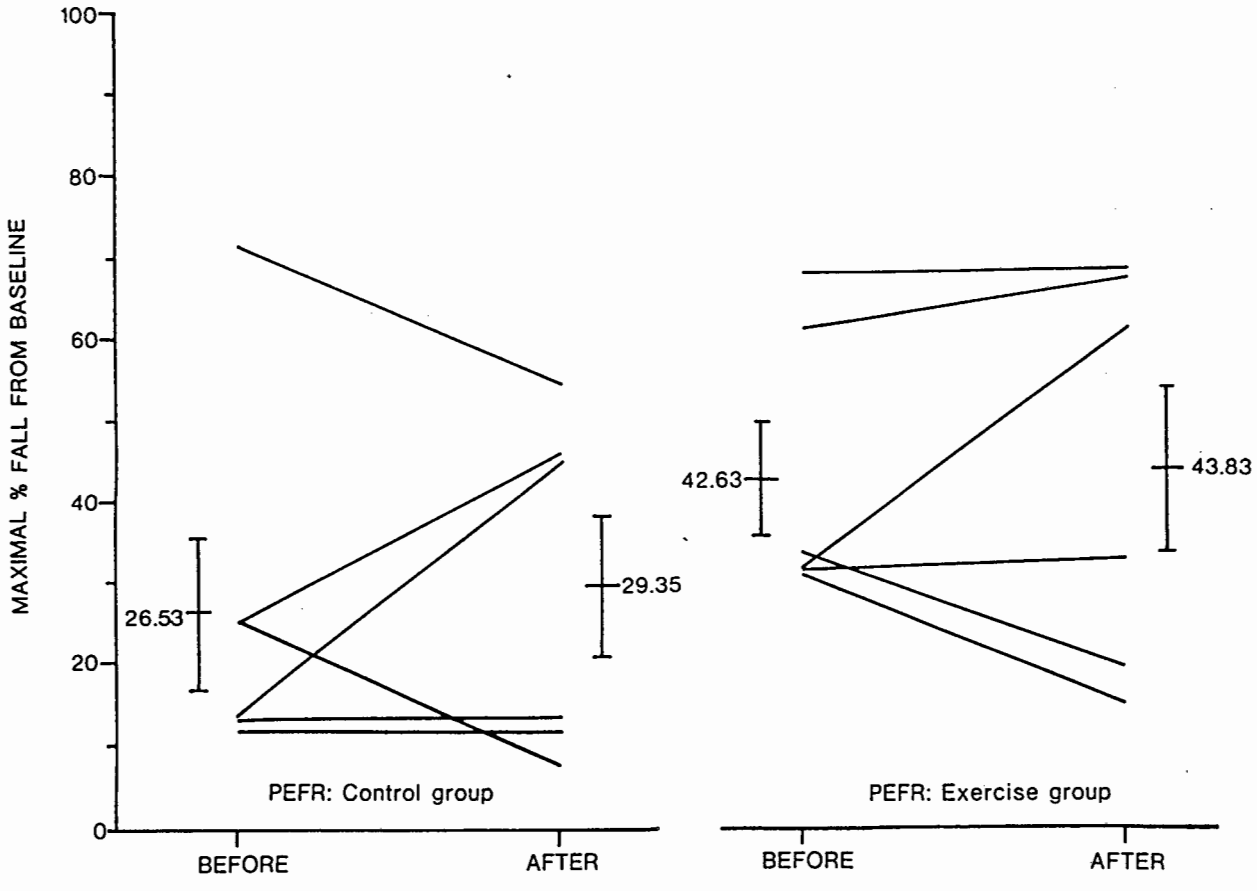


FIG 12: Individual results of maximal post-exercise falls in PEFR before and after the trial period. Means and SE are given. n=6 for each group.

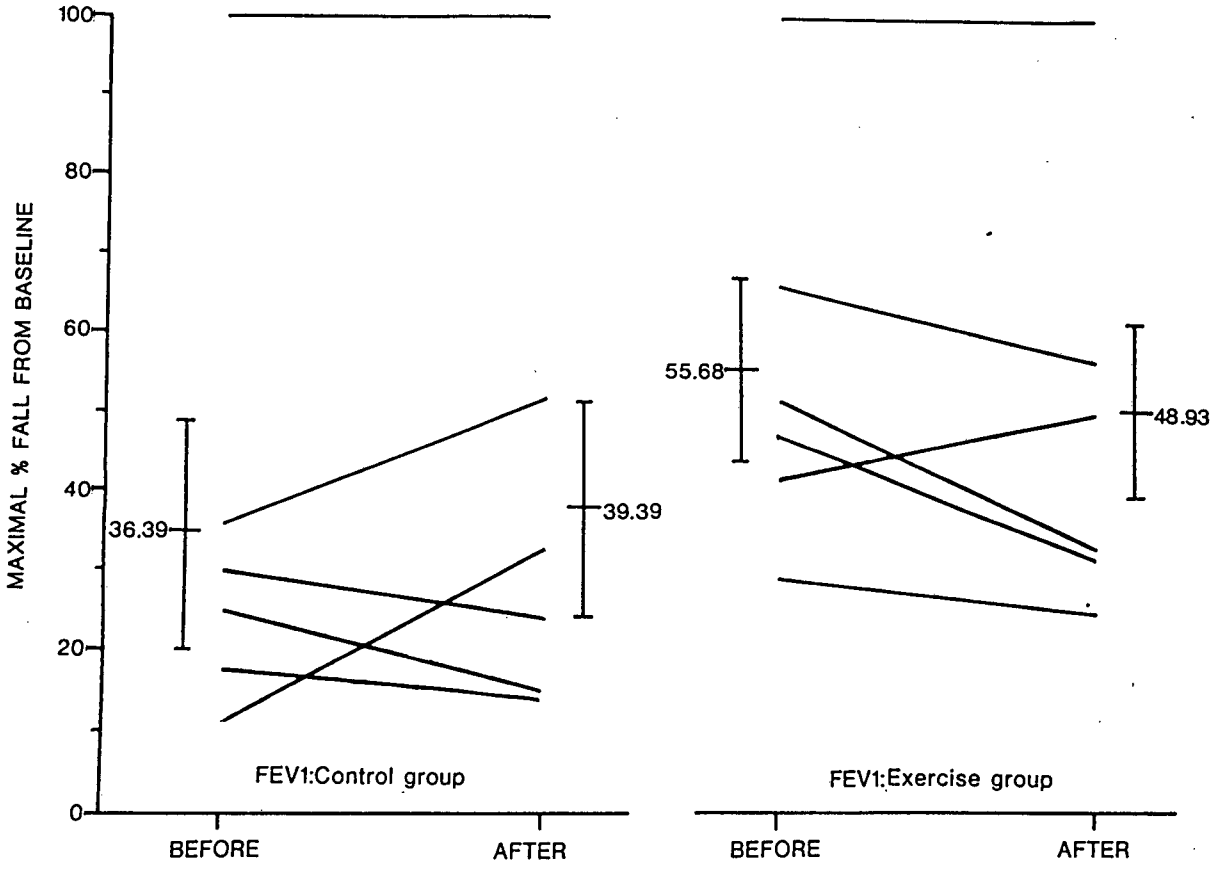


FIG 13: Individual results for maximal post-exercise falls in FEV1 before and after the trial period. Means and SE are given. n=6 for each group.

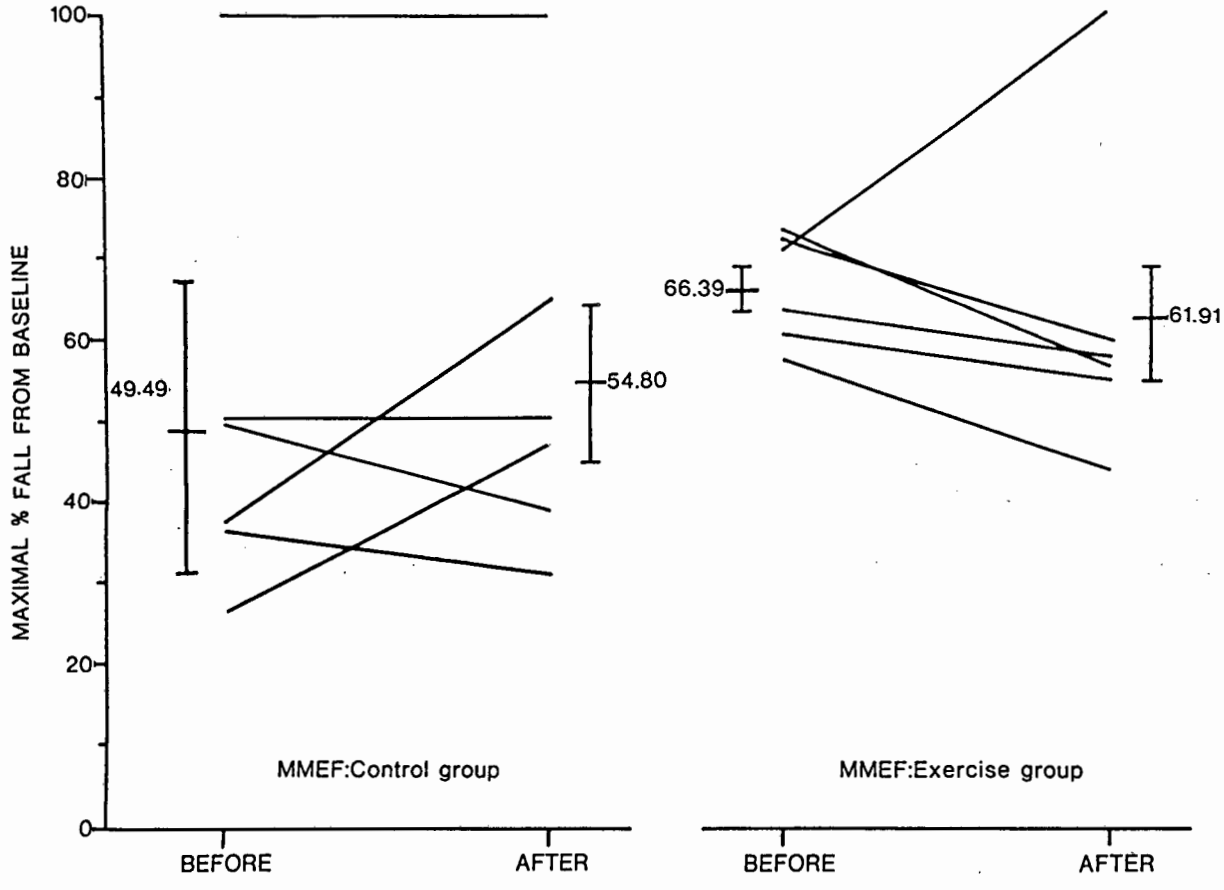


FIG 14: Individual results for maximal post-exercise falls in MMEF before and after the trial period. Means and SE are given. n=6 for each group.

Fig 10: Three hours later the subject inhaled fenoterol aerosol (two puffs of 200 micrograms each) and one sodium cromoglycate spincap (20 milligrams) five minutes prior to exercise. A drop in FEV1 and MMEF occurs in response to exercise, but this (<10% fall) is within normal limits. The maximal fall in these parameters occur four minutes after cessation of exercise.

Fig 11: On a different occasion the subject had lower baseline values for PEFR, FEV1 and MMEF. This resulted in a dramatic fall of these parameters in response to the same exercise stimulus. Administration of fenoterol aerosol resulted in rapid and effective bronchodilatation (arrow). These parameters were almost at baseline values three minutes later. FEV1 and MMEF reached levels above the pre-exercise value eight minutes after administration and remained high for at least a further twenty minutes.

4.1.Peak expiratory flow rate (PEFR) (tables 12a and 12b ; fig 12)

The mean percentage fall in PEFR was greater in the exercise group than in the control group for the March, July and December tests, but the differences are not statistically significant. In the exercise group, the mean values for percentage fall in PEFR for July and December were less than the initial fall but the differences are not statistically significant. However, the mean percentage fall in PEFR was significantly lower (p=0.02) in July compared with March in the control group. The intra-group differences are not statistically significant from each other.

4.2.Forced expiratory volume in one second (FEV1) (tables 12a and 12b; fig 13)

The FEV1 values are slightly higher than those of PEFR and follow a similar trend during the year. No statistically significant differences are evident within and between the groups.

4.3.Maximal mid expiratory flow rate (MMEF) (tables 12a and 12b ; fig 14)

This index of small airways obstruction showed higher mean percentage falls for the exercise group for all periods of measurement. The July and December values were lower than the initial fall in both groups. There were no statistically significant intra- and inter-group differences.

4.4.Forced vital capacity (FVC) (tables 12a and 12b)

This parameter showed the least perturbation and mean values were similar in both groups at all times. There were no significant intra- or inter-group differences.

A summary of all the variables measured during the study is shown in tables 13a, 13b and 14.

TABLE 12a : BASELINE AND MINIMAL POST-EXERCISE VALUES OF LUNG FUNCTION PARAMETERS FOR INDIVIDUAL SUBJECTS

1) PEFR

CONTROL GROUP

SUBJ	ABSOLUTE VALUES MAR		JUL		DEC		VALUES AS % PREDICTED MAR		JUL		DEC	
RA	260	190	280	210	370	200	75	55	79	59	99	54
SB	320	70	280	80	240	110	98	21	82	23	69	32
JB	410	270	410	400	460	400	116	76	114	100	121	105
WF	360	240	320	240	280	260	102	68	88	66	71	66
BF	370	270	340	300	440	390	113	82	100	88	126	112
FI	260	140	290	250	270	150	96	52	105	90	92	51
AVG	330	197	320	247	343	252	100	59	95	71	96	69
SD	61	80	50	105	94	122	15	22	14	28	24	31

EXERCISE GROUP

LA	270	110	410	180	470	400	80	32	117	51	130	111
SA	370	210	360	240	420	340	95	54	91	61	104	84
NJ	420	170	500	160	470	150	101	41	118	38	104	33
FM	320	80	360	140	365	120	86	22	95	37	91	30
CM	320	180	300	205	360	140	98	55	90	62	104	40
NS	330	230	510	350	520	350	94	66	131	90	127	85
AVG	338	163	407	212	434	250	92	45	107	57	110	63
SD	51	58	84	76	64	126	8	16	17	20	15	34

2) FEV1

CONTROL GROUP

RA	1.4	0.7	1.6	1.0	1.7	0.8	59	27	62	40	63	30
SB	1.4	0	1.4	0	1.1	0	65	0	61	0	49	0
JB	2.0	1.2	2.2	1.7	2.5	2.1	80	47	88	66	92	79
WF	1.7	1.2	1.6	1.1	1.9	1.4	76	55	66	47	72	55
BF	1.9	1.4	1.8	1.5	2.2	1.9	84	63	78	65	92	79
FI	1.6	0.8	1.8	1.6	1.3	0.9	88	46	96	85	65	43
AVG	1.7	0.9	1.7	1.1	1.8	1.2	75	40	75	51	72	48
SD	0.2	0.5	0.3	0.6	0.5	0.8	11	23	15	29	17	30

EXERCISE GROUP

LA	1.4	0.5	2.2	1.1	2.4	1.6	60	20	92	45	98	66
SA	2.1	1.3	2.1	1.5	2.2	1.7	81	52	82	59	85	65
NJ	1.9	0.6	2.8	0	2.6	0	61	20	90	0	76	0
FM	1.9	0.5	1.6	0.6	1.7	0.7	75	20	63	22	62	27
CM	1.7	0.8	1.9	1.1	1.4	0.7	80	39	88	51	64	33
NS	2.2	0.7	2.5	1.3	2.4	1.7	85	26	96	51	88	60
AVG	1.8	0.7	2.2	0.9	2.1	1.1	74	30	85	38	79	42
SD	0.3	0.3	0.4	0.6	0.5	0.7	11	13	12	22	14	26

Table 12a continued...

3) MMEF

CONTROL GROUP

SUBJ	ABSOLUTE VALUES MAR		JUL		DEC		VALUES AS % PREDICTED MAR		JUL		DEC	
RA	57	21	50	25	62	25	31	12	27	17	26	12
SB	47	0	65	0	38	0	28	0	37	0	21	0
JB	106	43	190	95	203	101	57	23	100	50	101	50
WF	61	36	50	25	67	41	33	20	26	13	32	20
BF	97	47	82	52	97	67	61	30	49	31	56	39
FI	80	24	92	69	49	25	64	19	71	53	35	18
AVG	75	29	88	44	86	43	46	17	52	27	46	23
SD	23	17	53	34	61	36	17	10	29	21	29	18

EXERCISE GROUP

LA	38	15	119	31	151	65	22	8	68	18	82	35
SA	102	39	118	50	107	61	50	19	56	24	50	28
NJ	62	18	128	37	92	0	29	8	58	17	39	0
FM	77	14	54	15	49	19	41	7	27	8	23	9
CM	74	25	76	30	45	20	44	15	44	17	25	11
NS	98	20	109	40	107	46	48	10	51	19	48	20
AVG	75	22	101	34	92	35	39	11	46	17	45	17
SD	24	9	29	12	40	26	11	5	18	10	22	13

4) FVC

CONTROL GROUP

RA	2.1	1.4	2.3	1.6	2.1	1.4	74	47	81	56	70	45
SB	2.1	0	2.2	0	1.6	0	83	0	85	0	60	0
JB	2.2	1.7	2.4	2.0	2.5	2.3	75	58	81	69	82	75
WF	2.6	2.2	2.5	1.6	2.8	2.5	99	86	91	59	94	84
BF	2.3	2.1	2.4	2.3	2.9	2.7	90	83	91	85	108	102
FI	2.1	1.6	2.3	2.1	1.9	1.5	101	74	104	99	83	66
AVG	2.2	1.5	2.3	1.6	2.3	1.7	87	58	89	61	82	62
SD	0.2	0.8	0.1	0.8	0.5	1.0	12	32	9	34	17	36

EXERCISE GROUP

LA	2.6	1.7	2.5	1.6	2.6	2.4	100	67	94	60	93	85
SA	2.7	2.5	2.9	2.7	3.0	2.7	95	85	101	91	102	92
NJ	2.9	1.4	3.7	2.5	3.8	0	81	40	102	69	97	0
FM	2.7	1.2	2.6	1.3	3.0	1.7	94	44	91	45	97	55
CM	2.2	1.4	2.6	1.8	2.2	1.2	94	59	109	76	87	49
NS	3.0	1.5	3.2	2.3	3.3	3.0	102	53	109	77	103	94
AVG	2.7	1.6	3.0	2.0	3.0	1.8	94	53	101	70	97	63
SD	0.3	0.5	0.5	0.6	0.6	1.1	7	18	7	16	6	36

Notes on table 12a...

i) The first of the pair of numbers under each month column (MAR: March; JUL: July; DEC: December) is the baseline value and the second is the minimal post-exercise value.
ii) SUBJ: Subject. Each subject's initials appears in the column beneath.
iii) PEFR: Peak expiratory flow rate (l/min).
FEV1: Forced expiratory volume in 1 second (l).
MMEF: Maximal mid-expiratory flow rate (l/min).
FVC: Forced vital capacity (l).
iv) AVG: Average.
SD: Standard deviation.

TABLE 12b : MEAN MAXIMAL POST-EXERCISE PERCENTAGE FALLS IN LUNG FUNCTION PARAMETERS

1) PEFR

	CONTROL GROUP			EXERCISE GROUP		
	MAR	JUL	DEC	MAR	JUL	DEC
MEAN	41.12	26.53 *	29.35	51.90	42.63	43.83
SD	19.89	22.83	21.00	15.80	17.15	24.52

2) FEV1

	CONTROL GROUP			EXERCISE GROUP		
	MAR	JUL	DEC	MAR	JUL	DEC
MEAN	49.35	36.39	39.39	60.27	55.68	48.93
SD	27.22	32.34	32.84	14.46	24.58	27.82

3) MMEF

	CONTROL GROUP			EXERCISE GROUP		
	MAR	JUL	DEC	MAR	JUL	DEC
MEAN	64.08	49.49	54.80	70.19	66.39	61.91
SD	59.98	26.44	24.38	9.24	67.45	19.48

4) FVC

	CONTROL GROUP			EXERCISE GROUP		
	MAR	JUL	DEC	MAR	JUL	DEC
MEAN	34.55	31.98	30.34	39.16	31.41	35.77
SD	24.49	35.57	35.88	16.71	13.15	35.66

n=6.

Note:
i) Significant p value for the paired t-test
Mar vs Jul : * $p < 0.05$
ii) MAR: March.
iii) Jul : July.
iv) DEC : December.

TABLE 13a : SUMMARY OF MEAN VALUES OF ALL VARIABLES MEASURED BEFORE AND AFTER THE TRIAL PERIOD.
MEAN DIFFERENCES (AFTER-BEFORE) AND 95% CONFIDENCE LIMITS OF THE MEANS ARE GIVEN

CONTROL GROUP

VARIABLE	AFTER	BEFORE	SD	MCF	MEAN DIFF	MCC	p CTL
vO2max	49.65	48.80	2.83	-1.98	0.85	3.68	0.49
vO2max Abs	1.96	1.88	0.09	-0.17	0.08	0.01	0.12
vCO2max Abs	1.96	1.68	0.19	-0.47	0.28	-0.09	0.03
R max	1.01	0.90	0.06	0.05	0.11	0.17	0.01
TM max	14.25	14.25	0.71	-0.71	0.00	0.71	1.00
lactate TP	9.33	9.17	0.98	-0.81	0.17	1.15	0.70
[LA]MSi	4.88	4.25	0.90	-0.26	0.64	1.54	0.14
PEFR mx fall	29.35	26.53	19.75	-16.50	2.83	22.96	0.74
FEV1 mx fall	39.39	36.39	12.96	-9.95	3.00	15.95	0.59
MMEF mx fall	49.49	54.83	12.00	-12.03	-5.34	11.95	0.98
FVC mx fall	30.34	31.98	13.34	-14.97	-1.64	11.69	0.78
Vi lm	47.67	45.85	7.71	-5.88	1.82	9.52	0.43
Vi lm meds	53.60	50.28	7.29	-3.96	3.32	10.60	0.32
HR @ Vi lm	185.83	179.17	14.59	-7.90	6.67	21.24	0.14
HR @ Vi lm m	185.67	187.83	14.34	-16.49	-2.17	12.15	0.73
HT	148.17	144.50	1.86	1.81	3.67	5.53	0.01
WT	39.53	38.95	1.00	-0.42	0.58	1.58	0.21
% body fat	16.30	17.37	0.52	-1.59	-1.07	-0.55	0.004
HT/WT/AGE	52.83	56.00	2.99	-6.15	-3.16	-0.17	0.05

n = 6.

TABLE 13b : SUMMARY OF MEAN VALUES OF ALL VARIABLES MEASURED BEFORE AND AFTER THE TRIAL PERIOD.
MEAN DIFFERENCES (AFTER-BEFORE) AND 95% CONFIDENCE LIMITS OF THE MEANS ARE GIVEN

	EXERCISE GROUP						
VARIABLE	AFTER	BEFORE	SD	MEF	MEAN DIFF	MEC	p EX
vO2max	54.03	49.03	3.24	1.76	5.00	8.24	0.01
vO2max Abs	2.23	1.88	0.14	-0.49	0.35	-0.21	0.003
vCO2max Abs	2.20	1.68	0.22	-0.74	0.52	-0.30	0.003
R max	0.99	0.89	0.10	0.00	0.10	0.20	0.06
TM max	16.50	15.25	1.08	0.17	1.25	2.33	0.04
Lactate TP	12.33	10.60	1.97	-0.30	1.67	3.64	0.09
[LA]MSi	3.97	4.03	1.33	-1.38	-0.05	1.28	0.92
PEFR mx fall	43.83	42.63	16.35	-15.13	1.20	17.53	0.87
FEV1 mx fall	48.93	55.68	9.87	-16.63	-6.75	3.13	0.16
MMEF mx fall	61.91	66.39	16.96	-21.26	-4.47	12.62	0.55
FVC mx fall	35.77	31.41	34.07	-29.68	4.35	38.38	0.77
Vi 1 m	49.10	49.62	6.12	-6.63	-0.52	5.59	0.78
Vi 1 m meds	56.32	52.13	7.31	-3.12	4.18	11.48	0.22
HR @ Vi 1m	181.83	190.00	10.50	-18.66	-8.17	2.32	0.02
HR @ Vi 1m	188.67	193.33	11.54	-16.20	-4.67	6.86	0.36
HT	155.67	152.33	2.34	0.99	3.33	5.67	0.02
WT	41.30	39.47	1.66	0.17	1.83	3.49	0.04
% body fat	13.58	14.37	0.73	-1.51	-0.78	-0.05	0.05
HT/WT/AGE	30.66	32.66	3.35	-5.35	-2.00	1.35	0.20

n = 6.

TABLE 14 : COMPARISON OF INTER-GROUP DIFFERENCES USING THE TWO SAMPLE T-TEST, BETA (TYPE II ERROR) AND N5%

VARIABLE	CMPRSN	BETA	N5%
vO2max	0.04	0.08	6
vO2max Abs	0.08	0.001	3
vCO2max Abs	0.09	0.21	8
R max	0.92	1.00	89617
TM max	0.07	0.06	5
Lactate TP	0.14	0.19	10
[LA]MSi	0.32	0.85	66
PEFR mx fall	0.88	0.91	607
FEV1 mx fall	0.20	0.36	11
MMEF mx fall	0.61	0.97	88
FVC mx fall	0.70	0.63	120
Vi lm	0.59	0.79	70
Vi lm meds	0.84	0.95	505
HR @ Vi lm	0.09	0.14	8
HR @ Vi lm m	0.75	0.88	191
HT	0.79	0.98	271
WT	0.15	0.26	10
% body fat	0.46	0.66	35
HT/WT/AGE	0.54	0.82	3925

n = 12.

Notes on tables 13a, 13b and 14 :

i)	n = 6 for each group.	
ii)	AFTER:	Final value after trial period.
iii)	BEFORE:	Initial value before trial period.
iv)	MEAN DIFF:	Mean difference between final and initial values.
v)	p EX, p CTL:	Paired t-test for exercise and control groups.
vi)	MCF,MEF:	Lower boundary (floor) of 95% confidence limits for control and exercise groups.
vii)	MCC,MEC:	Upper boundary (ceiling) of 95% confidence limits for respective groups.
viii)	CMPRSN:	Two sample t-test
vix)	BETA:	Type II error calculated assuming an alpha of 0.05.
x)	N5%:	Optimistic minimul number of subjects required in each group for beta=0.05 assuming means and SD's remain unchanged.

Variables measured during maximal treadmill test:

xi)	vO2max:	Maximal oxygen consumption expressed in ml/kg/min.
xii)	vO2max Abs:	Absolute VO2 max (l/min).
iii)	vCO2max Abs:	Absolute maximal output of CO2.
xiv)	Rmax:	Maximal Respiratory exchange ratio
xv)	TM max:	Maximal treadmill speed reached.
xvi)	Lactate TP:	Lactate turnpoint (km/h).
xvii)	[LA]MSi	Plasma lactate concentration corresponding to maximal speed of initial treadmill test (mmol/l).

Variables measured during or after the asthmagenic treadmill test:

xviii)	PFRmx fall:	Maximal fall in PEFR (l/min).
xix)	FEV1 mx fall:	Maximal fall in FEV1 (l).
xx)	MMEF:	Maximal fall in MMEF (l/min).
xxi)	FVC:	Maximal fall in FVC (l).
xxii)	Vi 1m:	Ventilation (l/min) corresponding to last minute of initial test
xxiii)	Vi 1m meds:	Ventilation (l/min) as above with pre-medication.
xxiv)	HR @ Vi 1m:	Heart rate (beats/min) corresponding to last minute of initial test.
xxv)	HR @ Vi 1m m:	HR as above with pre-medication.

Anthropometric measurements:

xxvi)	HT:	Height (cm).
xxvii)	WT:	Weight (kg).
xxviii)	HT/WT/AGE:	Ratio of height/weight/age.

5.RESULTS OF QUESTIONNAIRES

5.1 Result of the first questionnaire

A questionnaire was sent to parents of the subjects before the beginning of the study. Parents were questioned about their son's asthma, physical activity and attitudes concerning these points.

Letters (eg.a) listed under 'frequency' are explained at the end of the questionnaire.

The questions , and response frequency are listed below. Response from ten out of twelve parents were obtained. The questionnaires are listed in Appendix I.

QUESTION	FREQUENCY
1. Why did you allow your son to participate in the study ?	
i) We want his asthma to improve.	9
ii) He likes physical exercise.	5
iii) We would like him to do more physical exercise than before.	4
iv) Because we have no objections.	0
v) Other.	0
2. Has your son participated in any other study/trial before ?	3
3. How long has your son had asthma ?	
i) Since a baby.	8
i) More than 5 yrs.	1
iii) Between 2 and 5 yrs.	1
iv) Less than 2 yrs.	0
v) Other.	0
4. Over the past year his asthma has been	
i) Improving.	5
ii) Worsening.	0
iii) The same.	0
iv) Varies according to the season.	5
v) Variable and unpredictable.	3

5. How many days has your son been absent from school last year ? (Median: 9; Avg: 10)

6. On average how many times does your son get a cold/flu/chest problems a year ? (3;5;8;9 times; a)

7. How would you compare your son's physical activity with that of your other children ?

i)	No other children.	1
ii)	More.	4
iii)	About the same.	4
iv)	Less.	1
v)	Don't know.	0
vi)	Details.....	

8. How would you compare your son's physical activity with that of his friends ?

i)	More.	2
ii)	About the same.	7
iii)	Less.	0
iv)	Don't know.	1

9. Does your son play regular sport at school ? 4

10. If yes, give details.... b

11. Is your son's physical activity limited at school or at home because of

i)	Advice of teacher.	0
ii)	Advice of doctor.	0
iii)	Decision of parents.	1
iv)	He does not want to.	2
v)	Afraid of getting asthma.	0
vi)	Other....	c

12. Is your son a member of a sports team ? 3
If yes, give details....

13. Does your son take part in athletics ? 3
If yes, give details.... d

14. Does anyone else in the family play sports regularly ? 3
If yes, give details.... e

15. Does your son participate in recreational activities that involve physical exercise.

i) Bicycling.	9
ii) Swims.	7
iii) Other... (scouts)	1

16. If he is not active enough, what are the reasons ?

i) Afraid of getting asthma	1
ii) Not interested.	0
iii) No facilities.	2
iv) Other interests.	1
v) I don't know.	1
vi) Other...	f

17. Has your son been admitted to hospital for an asthma attack during the past 2 years ? 4
If yes, explain.... (admission for 1-2 days.)

18. Mark off the statements which you think is correct.

i) Physical activity is important for one's health.	9
ii) Physical activity can help improve some illnesses.	9
iii) Physical activity is important to control one's weight.	6
iv) Physical activity is not needed by all.	1
v) It is more important for children to be fit than adults.	2
vi) Adults don't need to be fit.	0

19. As parents

i) We are reasonably fit.	5
ii) We don't have time to get fit.	1
iii) We don't have the necessary facilities.	4
iv) We make a point of doing regular exercise.	1
v) It is not important for us to be fit.	1
vi) We are too old to become fit.	1
vii) Other....(no response)	1

Other responses.

a: Q6, Other answers were:'average', 'often', 'frequently', 'every second week'.

b: Q10, Sports played:

Soccer	LA, NS, JB, WF.
Rugby	NS.
Swimming	NS.
Gymnastics	NS.

c: Q11, 3 reported that they did not limit their son (LA, NJ, FM).
1 reported school activity was P.T. only (SA).

d: Q13, 3 performed well in athletic events.
1 subject: 100m; 200m; long jump (NJ).
1 " : 100m (FM).
1 " : 1500m; 3000m (NS).

e: Q14, In 3 families, siblings play regular sports (SA, FM, NS).

f: Q16, 1 subject: no limitation to activities (FM).
1 " : no sports offered at school (FI).
3 subjects: no reponse given.

5.2 Result of second questionnaire

A questionnaire was sent to all subjects' parents at the end of the study. Different questionnaires were formulated for each group. Questions were asked about clinical asthma, new physical activities and attitude to these factors. In most instances, the subject and parent(s) answered the questions together.
Questions and responses are listed below. All subjects replied.

5.2.1 Questionnaire to exercise group

	YES	NO	DON'T KNOW
1) SINCE THE TRAINING PROGRAMME HAVE YOU NOTICED :			
improvement in asthma	5		
less frequent attacks	6		
increased physical activity	6		
no difference in asthma	1		

2) HAS YOUR SON STARTED ANY NEW PHYSICAL ACTIVITIES SINCE THE TRAINING PROGRAMME BEGAN ?

YES: 2 (cycling; karate)

3) HAS YOUR SON'S ATTITUDE TO HIS ASTHMA CHANGED ?

i) More aware: 1 subject became more aware of asthma as an illness.

ii) Always been aware: 3 subjects.

iii) Less aware: 2 subjects were less aware because of less frequent asthmatic episodes.

4) HAS YOUR ATTITUDE TO ASTHMA CHANGED ?

i) More aware: 1 parent of subject who answered 'i' in previous question.

ii) Always aware: 2 groups of parents.

iii) less aware: 3 responses, reasons same as 'iii' in previous question.

5) HAS THERE BEEN ANY CHANGE IN YOUR SON'S :

i) mood: YES: 2 subjects (happier, more eager to play games).

NO: 4 subjects.

ii) need for medicines (oral): YES: 2: less medication.

NO: 4.

iii) need for inhalers (Berotec): YES: 3: less ("less often"; don't need" "never uses")

NO: 3.

iv) school attendance: YES: 1: missed fewer days.

NO: no change.

5.2.2. Results of questionnaire to control group

	SAME	IMPROVE	WORSE	DON'T KNOW
1) HOW HAS YOUR SON'S ASTHMA BEEN:				
i) SEPT.-DEC. 1985 :	3	3		
ii) JAN.-MARCH 1986 :	3	3		

	SAME	BETTER	WORSE	DON'T KNOW
2) HOW HAS YOUR SON'S ASTHMA BEEN AFTER EXERCISE ?	2	4 (seasonal in 1)		

3)
HAS YOUR SON STARTED ANY NEW PHYSICAL ACTIVITIES SINCE SEPT. 1985 ?

YES: 3 subjects 1: karate; soccer (FI).
1: running (WF).
1: cycling (JB).

4) HAS YOUR SON'S ATTITUDE TO HIS ASTHMA CHANGED ?

i) More aware of asthma as a chronic illness (3).

ii) Always been aware: 2.

ii) Less aware: 1.

5) HAS YOUR ATTITUDE TO ASTHMA CHANGED ?

i) More aware of asthma as a chronic illness (2).

ii) Always aware: 3.

iii) Less aware

6) DID RUNNING ON THE TREADMILL AFFECT YOUR SON'S ATTITUDE TO EXERCISE ?

YES: 3 stated that they enjoyed treadmill running.

NO: 3 (1 continued school PT as before.)

7) WOULD YOU HAVE LIKED TO PARTICIPATE IN THE EXERCISE PROGRAM ?

YES: 6.

8) IF YOU HAD THE OPPORTUNITY TO PARTICIPATE IN AN EXERCISE PROGRAM, WOULD YOU LIKE TO JOIN ?

YES: 6.

9) HAS THERE BEEN ANY CHANGE IN YOUR SON'S:

i) mood: YES: 3:

NO: 2:

ii) need for medicines: YES: 2 (BF needed less, WF needed more).

NO: 4.

iii) need for inhaler (Berotec): YES: 2 (WF needed more, BF needed less).

NO: 4.

iv) school attendance: YES: 3 (1 missed more days, 2 missed fewer).

TABLE 15 : SCORES OF DAILY DIARY VARIABLES FOR SEPTEMBER

		NIGHT WHEEZE	NIGHT COUGH	DAY WHEEZE	DAY ACTIVITY	SMILE	DOSES OF BEROTEC INHALER
CONTROL GROUP	TOTAL	86	78	71	67	159	334
	MEAN	17.2	15.6	14.2	13.4	31.8	66.8
	SD	10.4	5.9	13.3	14.5	4.0	106.6
EXERCISE GROUP	TOTAL	35	29	37	36	165	405
	MEAN	7	5.8	7.4	7.2	33	81
	SD	7.1	5.7	7.6	7.5	4.5	65.5

Note:
Night cough Exercise vs Controls:
p=0.03 for the two sample t-test.

6.Daily diaries (table 15)

Five subjects in each group completed the daily diaries for September. The compliance fell dramatically for the rest of the trial period resulting in insufficient data for meaningful analysis.

The symptoms were scored from 0-3 (good-worst), and additional medication was recorded. A `smile chart' indicated the general mood (or morbidity) of the subject during the day and was scored 1-3 (happy-sad). Space for additional comments was given, but was not used very often. The number of puffs of fenoterol aerosol used per month was recorded for each subject.

The control group had approximately double the scores of the exercise group for the indicators of clinical asthma (night wheeze, night cough and day wheeze). The only statistically significant difference was for night cough ($p=0.03$).

The mean number of fenoterol puffs inhaled was greater in the exercise group. One subject in each group substituted cromoglycate spincaps for fenoterol aerosol. One subject in the control group (WF) had an exacerbation of asthma and required oral prednisone. Fenoterol aerosol was discontinued during the month.
Both groups indicated that they were reasonably 'happy' during September.

7.Medication prescribed at the Red Cross War Memorial Children's Hospital (table 16)

The record of the medication prescribed at the Hospital provided an independent barometer of a subject's clinical asthma.

All the subjects were prescribed sodium cromoglycate spincaps (Lomudal) and fenoterol aerosol (Berotec) at the beginning of the study.

Two subjects in the exercise group (LA and FM) and one in the control group (BF) were no longer prescribed cromoglycate at the end of the study. One subject (SA) was taken off fenoterol aerosol and three (LA, FM and NS) were advised to use this when necessary only. This is in contrast to the control group who were all prescribed regular aerosol medication.

TABLE 16 : MEDICATION PRESCRIBED AT THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL

NAME	LOM SP		BER IN		EU RET		THEO		PRED		BECN	
	S	D	S	D	S	D	S	D	S	D	S	D
EXERCISE GROUP												
LA	+	0	+	PRN			+	0	10	0	+	+
SA	+	+	+	0							+	+
NJ	+	+	+	+			+	+			+	+
CM	+	+	+	+	+	+					+	+
FM	+	0	+	PRN							+	PRN
NS	+	+	+	PRN	+	+					+	+
CONTROL GROUP												
RA	+	+	+	+					20	20		
SB	+	+	+	+	+	+					+	+
JB	+	+	+	+	+	+					+	+
WF	+	+	+	+			+	+	20	20		
BF	+	0	+	+	+	+						
FI	+	+	+	+								

Notes on table 16:

The first 6 subjects are those from the exercise group.
D : December.
S : September.
+ : Regular dosages required.
0 : Not prescribed.
PRN : Taken when symptomatic only.
10; 20 : Milligrams alternate days.

BECN : Beconase aqueous nasal spray.
BER IN: Berotec aerosol inhaler.
EU RET: Euphyllin retard.
LOM SP: Lomudal spinhaler.
PRED: Prednisone tablets.
THEO: Theodur tablets.

Subject SB was prescribed Ventolin Spandets on both dates.
Subject FI was prescribed Ventolin tablets (4mg) on both dates.

Only LA was prescribed less oral medication at the end of the study. It is noteable that he did not require prednisone after the trial period.

8.Allergy tests

Almost all the subjects (except JB) proved to be atopic using both the radioimmunosorbent test (RAST) and skin-prick methods used at the Red Cross War Memorial Children's Hospital.

The most common allergens for which the subjects displayed atopy were housedust and housedust mite (Dermatophagoides pteronyssinus). Nine subjects showed positive results for each allergen: 5 subjects in the exercise group and 4 in the control group. Two subjects in the exercise group and one the control group were allergic to grass.

CHAPTER V

DISCUSSION OF RESULTS

DISCUSSION OF RESULTS

1.ANTHROPOMETRIC MEASUREMENTS

Both exercise and control groups were pre-adolescent (13 ± 0.9 yrs and 11.5 ± 1.25 yrs respectively) and were growing rapidly during the period of measurement. It is most likely that the exercise group was taller than the control group because they were older.

The most likely reason for the mean weights being similar despite the significant height difference was that the control group was fatter than the exercise group before and after the trial period.

The statistically significant decreases in percent body fat (exercise group: $p=0.05$; control group: $p=0.004$) is small in absolute terms: 0.8 % and 1.1 % respectively. The coarseness of the measuring technique (skinfold calipers) detracts from the statistical results and it is probably safe to say that no appreciable decrease in percent body fat occurred. The negative trend of the values could reflect seasonal and environmental factors, for example the subjects were slightly fatter in winter when baseline measurements were made. Nutrition and daily energy expenditure are probable factors which varied during the year.

Height/weight/age was chosen as an index of nutritional status. Waterlow et al (1977) devised a parameter which combines height/age and weight/age predictions to relate weight to height, giving an indication of general health and nutritional status. The anthropometric measurements are reflected in this parameter and the control group has a higher mean centile than the exercise group. This indicates that the control group was shorter and

fatter than the exercise group. Both groups grew taller and thinner during the year, as to be expected during puberty. These changes resulted in a small decrease in the height/weight/age centile in the control group but not the exercise group. The coarseness of measurement inherent in reading centiles from growth charts diminishes the confidence with which one can interpret these results. Computation of this parameter from data obtained from standard growth charts such as the National Centre of Health Statistics tables (NCHS, Ross Laboratories, Columbus, Ohio, 1976) would be more appropriate when anthropometric changes are taking place over a period of time.

The high centiles of some subjects do not necessarily indicate good nutrition as is the case for 'normal' children. Subject RA was on daily steroid medication and was overweight as a result. His high centile rating (80) indicates that centile rating cannot be applied to all asthmatic children, especially those on corticosteroids.

2.MEASURMENTS DURING MAXIMAL TREADMILL TESTING

2.1.Maximal treadmill speed

The exercise group significantly improved their maximal treadmill speed reached after the training programme ($p=0.04$). The emphasis on running during training resulted in a degree of specificity of training which is to be expected. Improvement of other parameters including reduced oxygen consumption and heart rate during sub-maximal exercise indicate a more generalized training effect.

The control group did not perform better after the trial period and the difference between the intra-group changes with training was significant ($p=0.05$).

2.2 Relative maximal oxygen consumption

Five of the six subjects in the exercise group showed an increase in relative vO_2 max after training. The mean improvement of 5 ml kg^{-1} min^{-1} is statistically significant ($p=0.01$).

This finding is in agreement with results published by Itkin and Nacman (1966), Bundgaard et al (1982), Orenstein et al (1985) and Ramazanoglu and Kraemer (1985).

2.3.Absolute maximal oxygen consumption

Almost all the subjects showed an improvement in absolute vO_2 max which can be ascribed to the increased muscle mass accompanying growth. However, the mean improvement in the exercise group (0.35 ± 0.14 l min^{-1} ; $p=0.003$) is significant whereas that of the control group (0.08 ± 0.09 l min^{-1} ; $p=0.12$) is not. The difference between the improvements is almost significant ($p=0.08$).

The type II error (0.001) implies that measurement of this parameter is associated with a statistically small chance of failing to find a real difference between the two groups. The small sample sizes and the increase in absolute vO_2 max in both groups contribute to this finding. Expression of vO_2 max relative to body weight removes some of the contribution of growth (weight) to this parameter.

2.4.Absolute maximal carbon dioxide production

The increase in this value accompanies the improvement in maximal absolute oxygen consumption. Statistically significant increases occur in both groups (exercise group: $p=0.003$; control group: $p=0.025$). The difference between the improvements is not significant ($p=0.09$).

The growth of the children and a technically 'better' maximal test probably contributes to this result.

2.5.Respiratory exchange ratio at maximal oxygen consumption

The maximal respiratory exchange ratio (RER) improved in both groups after the trial period. Ths is statistically significant in the control group (p=0.01) and is almost significant in the exercise group (p=0.06).

This result implies that both groups hyperventilated to a greater extent during the end of the final maximal test and suggests that both groups used greater cardiorespiratory effort in the latter test. It is likely that both groups were prepared to run to a greater percentage of their 'true maximum' after becoming acquainted with the treadmill and respiratory apparatus.

2.6.Blood lactate concentration

The blood lactate concentration at the maximal speed of the initial treadmill test is compared to the blood lactate concentration for the corresponding speed during the final maximal test.

The blood lactate concentration did not show a consistent trend in the trained group and the final value was slightly lower than the initial value. The difference (0.06 mmol l^{-1}) is not significant (p=0.92). In the control group the mean value did not change significantly (0.64 mmol l^{-1}; p=0.14) and there is no appreciable difference between the intra-group changes.

Blood lactate concentration decreased in response to training in three subjects SA, CM and FM: the first two subjects also demonstrated increased maximal treadmill speed and increased vO_2 max;

FM showed none of these improvements. These results confirm the improved fitness of SA and CM. NJ and NS showed increased lactate concentrations despite improved maximal treadmill speed and relative maximal oxygen consumption. Inbar and Bar-Or (1986) cited previous studies and confirmed that age-related differences in anaerobic performance could not be explained by differences in body size or in active muscle mass alone. The rapid growth of these subjects (NJ and NS) is therefore not responsible for the temporal increase in blood lactate concentration. It is well documented that pre-pubescent children have a lower glycolytic capacity than adults (Eriksson, Gollnick and Saltin, 1973 ; Eriksson, Karlsson and Saltin, 1971), but reasons for this have yet to be established.

Tanaka and Shindo (1985) found that maximal blood lactate levels increased with age and that the running speed at the blood lactate threshold was greatest for 10-11 yr olds (11.4 km h^{-1}). The maximal blood lactate concentrations are lower than the values found by Tanaka and Shindo (1985). This can be explained by differing times of sampling: The above authors sampled at 3 and 5 minutes after exhaustive track running whereas I sampled at the maximal speed reached during the initial test. The delay in efflux of lactate from the working muscle into the venous circulation explains the different results.

2.7.Lactate turnpoint

Visual determination of the lactate turnpoint is both rapid and simple, but is limited because of its subjectivity. An objective method used by Tanaka and Shindo (1985) was modified to fit the data: The warm-up run prior to the exercise test probably raised

the baseline blood lactate concentration to approximately 2 mmol l^{-1} in 6 subjects; 2.5 mmol l^{-1} was chosen as the criterion for lactate turnpoint in these subjects.

The objective method used is not entirely satisfactory as it is unique to this study and is limited in its comparison with other studies. Computer-calculated lactate turnpoints were not reliable as many values were obviously different from visually determined turnpoints.

An important point is that in response to training, no significant change in lactate turnpoint was evident from both methods used. It is possible that no improvement in oxygen-independent ('anaerobic') metabolism occurred after training despite an improvement in maximal aerobic capacity (vO_2 max). However, the improvement in turnpoint as determined visually almost reached significance level ($p=0.09$). The small sample group may be responsible for this finding.

It is well documented that 'anaerobic' performance is age-related and cannot be explained by changes in body size or active muscle mass. It seems that qualitative characteristics of muscle change with maturity of the individual (Inbar and Bar-Or, 1986). However, identification of the stimuli for this change or conditions under which an individual acquires adult 'anaerobic' characteristics remains a mystery. It is possible that these factors were operating in some subjects during the trial period and may have altered the individuals' lactate response to maximal exercise. It is unknown what time period is required for maturity of the glycolytic pathway and this further confounds interpretation of these results.

Astrand (1952) reported that compared to adults, glycolysis in children plays a smaller role in energy production during strenuous exercise (cited by Eriksson, Gollnick and Saltin, 1973). This has since been accepted by most exercise physiologists. However, results in different studies in this direction have been somewhat confusing: A study in children by Bell et al (1980, cited by Tanaka and Shindo, 1985) indicates that in children less lactate forms and accumulates in contracting muscles for the same relative workload as compared with adults. Eriksson, Gollnick and Saltin (1973) found that muscle lactate concentrations in boys were higher after training at all relative cycle ergometer workloads. The authors suggested that the increased glycolytic activity and oxidative capacity of skeletal muscle induced by training combined to produce greater lactate production and work capacity. In contrast to muscle, blood lactate levels tended to be lower at heavier workloads after training. While it seems that children have lower muscle glycolytic capacity, the effect of training on oxygen-independent metabolism remains to be fully elucidated. The mean blood lactate concentration corresponding with the maximal speed reached during the initial treadmill test did not change significantly in response to training (table 8). The different ages and muscular maturity of the trained subjects may have further confounded the results.

3.Summary of parameters measuring fitness (table 11)

3.1.Exercise group

In response to training, the exercise group showed significant mean improvements in absolute and relative vO_2 max, maximal treadmill speed reached and a decrease in heart rate during

submaximal (asthmagenic) treadmill running. These findings reflect improved maximal aerobic capacity, increased treadmill work capacity and increased cardiovascular fitness repectively. Measurement of blood lactate and lactate turnpoint did not show any significant changes. The reasons for this have been discussed.

3.2.Control group

Almost all subjects showed a small increase in absolute vO_2 max ($p=0.12$), which can be explained by the growth of the boys. The mean relative vO_2 max, maximal treadmill speed reached and heart rate during submaximal exercise remained essentially unchanged after the trial period. After the trial period, the RER improved in all the control subjects ($p=0.01$) but only one subject reached a higher maximal treadmill speed. This suggests that the subjects expended greater respiratory effort for a similar workload during the final test (assuming similar diets for before and after tests). As expected, the lactate turnpoint and blood lactate values did not change after the trial period.

4.Lung function tests

It is not possible to discuss meaningfully mean group trends because not all subjects were able to run for the prescribed duration; that is the asthmagenic stimuli were not consistent for the subjects. The wide range in severity of asthma, the variability of the asthmatic response and differing running abilities contribute to the difficulty in comparing the two groups.

I shall therefore briefly discuss temporal group trends and inter-group differences.

Ambient conditions in the laboratory were partially controlled by an air-conditioning unit. The ambient temperature ranged from 21-26 °C and the humidity from 50-60%. It is possible that environment conditions outside the laboratory influenced the lability of the subjects' airways. This was illustrated when SB's moderately severe asthma was exacerbated when he travelled to the laboratory on a cold wintry day. He normally travelled to the laboratory by bus, but on one occasion he missed the bus and decided to run to the laboratory (±3 km) despite not having taken his medication. He arrived in acute bronchospasm and needed nebulised medication. He was very disappointed when he was not allowed to run on the treadmill !

4.1.PEFR

The exercise group showed greater post-exercise falls in PEFR than the control group. This is evident for all three periods of measurement. This bias was apparent from the outset despite the differences not being statistically significant (p=0.15): The range in maximal percentage falls was 43.55 - 75.00 % in the exercise group and 26.92 - 79.12 % in the control group and the median falls were 43.65 % and 33.74 % respectively, indicating that the exercise group showed greater post-exercise bronchoconstriction than the control group.

The mean pre-exercise baseline was higher in the exercise group than the controls for all three asthmagenic tests. This pattern is reflected in FEV1 and MMEF responses and provides additional evidence that the exercise group had more severe EIA than the controls.

The lower mean baseline in March probably contributed to the larger mean percentage fall when compared with the July and December results.

4.2.FEV1

The March mean falls in FEV1 are higher than the subsequent values in both groups with a significant difference between the March and July mean falls in the control group ($p=0.02$). The most likely reason for this is that the March mean baseline was smaller than the July value.

Values of 100% (fall) were recorded if a subject could not exhale successfully into the spirometer at a required time-interval after cessation of exercise. This occurred in one subject in each group: subject NJ in July and December and SB for all three periods. This resulted in an equally raised mean percent fall in FEV1 for each group during the July and December tests. The exercise group showed consistently greater post-exercise percent falls in FEV1 than the control group, confirming what the PEFR results showed.

4.3.MMEF

The July and December mean percentage falls were lower than the March values in both groups. The higher mean baseline values during July and December probably contribute to this result. However, no significant differences were noted between or within the groups. These values are more comparable than PEFR or FEV1 and both groups demonstrate a large degree of small airways obstruction.

4.4.FVC

This variable expectedly showed the least change in response to an asthmagenic exercise stimulus in both groups. The mean values were very comparable within and between both groups but the range varied greatly (eg. 4.89 - 100 % fall in the control group in July). The mean values ranged between 30 - 39 % for all periods and this represents relatively minor perturbations when compared to the other parameters (PEFR, FEV1, MMEF).

4.5.Summary

Balfour-Lynn, Tooley and Godfrey (1981) showed that EIA is a sensitive indicator of clinical asthma, but has no prognostic significance in the symptom free patient. The results of 5 subjects confirm this finding. A reduction in medication without objective improvement in EIA was shown by 2 subjects: a slight improvement in clinical asthma did occur (reported fewer asthmatic attacks). However, the asthmagenic treadmill exercise without premedication may have been too great a stimulus to detect the improvement.

5.Discussion of results of questionnaires

5.1.Pre-trial questionnaire

The responses will be dealt with separately:

Q1: Almost all parents wanted their child's asthma to improve; this (rhetorical) question need not have been asked. Four answered that their son liked exercise and four wanted their son to be more physically active (JB, RA, NJ, NS and SA, CM, RA, FI respectively). This indicates that the subjects were a selected group from the outset and were reasonably well motivated. The

responders were represented in both groups.

Q2: Numerous trials have been conducted at the Red Cross War Memorial Children's Hospital's Allergy Clinic and I wanted to know whether the same subjects tended to volunteer. However, only three subjects had taken part in previous trials.

Q3: Eight subjects had virtually lifelong asthma (obstructive airways disease) and no subject had recently developed the condition (< 2 years).

Q4: Five parents thought that their son's asthma was improving. In retrospect, most were correct as four showed improved clinical and exercise-induced-asthma (LA, SA, JB, WF).

Five answered that their son's asthma varied according to the season (SA, NJ, CM, RA, JB), whereas three found their son's asthma unpredictable (NJ, NS. FI).

Q5: The range of absenteeism from school varied greatly (1 day - 3 weeks), representing exacerbations of asthmatic episodes or respiratory tract infections.

Q6: The answers did not correlated well with Q5; most parents knew the number of days their son was absent from school, but not all could recall the frequency of repiratory tract infections. The control and exercise groups were absent for a mean of 11 days and 6 days respectively.

Q7: It is noteable that only one parent (of WF) felt that their son was less active than the other siblings. Four parents actually thought that their sons were more active despite their asthma (LA, SA, NS, RA).

Q8: Nine parents thought that their son's activity was the same or more than that of their friends. These two questions indicate that most subjects were (at least) as active as non-asthmatic children.

Q9: Only four children played regular sports at school (LA, NS, JB, WF) whereas four parents said that their sons did not (RA, FI, SA, CM). Two parents did not respond.

Q10: The sport played most regularly was soccer (LA, NS, JB, WF).

Q11: Three parents indicated that they did not limit their son (LA, NJ, FM) and two parents allowed their son to decide (CM, NS). It is heartening to note that no decision of doctors nor teachers led to the limitation of any subject's physical activity.

Q12: LA, NS and WF belonged to school sports teams.

Q13: NJ and FM were good 100m sprinters and NS was a good middle-distance runner (1500 - 3000m). They were often placed in the top four positions in school athletic meetings.

Q14: A small number of families were physically active (SA, FM, NS).

Q15: Almost all the subjects cycled or swam or both. This probably reflects the activities of non-asthmatic children as well.

Q16: Only one parent thought that their son (RA) limited his exercise because of fear of precipitating an attack. Three parents answered that no sporting facilities were available (WF, FI, CM).

Q17: SA, RA and WF had been admitted to medical casualty at the Red Cross War Memorial Children's Hospital for one day and NJ had been admitted for two days because of asthmatic attacks.

Q18: Most parents felt that physical activity was important for one's health and could improve illnesses (9 responses).

Q19: Five parents thought that they were reasonably fit whereas four did not have necessary facilities available.

In summary, it appears that most subjects were physically active before the trial period. However, families indicate that they would be more active if sporting facilities were available.

5.2.Second questionnaire

I shall briefly discuss the results of the questionnaires which were completed after the trial period.

5.2.1.Questionnaire to the exercise group

Q1) All subjects experienced less frequent asthmatic attacks after the training programme. The physical activity (apart from the training programme) of the boys also increased.

Q2) CM started cycling and SA attended karate classes since the beginning of the training programme. Most of the subjects became generally more active in their daily lives. It seems likely that their improved fitness allowed them to increase their participation in physical activities, as most were enthusiastic about exercise at the onset of the study.

Q3) The following two questions were slightly confusing and further questioning was required to clarify the answers.

FM became more aware of asthma as an illness whereas SA, CM and NS had always been aware of their condition. LA and NJ were less aware because of less frequent asthmatic episodes.

Q4) FM's parents were more aware of asthma as an illness. Similarly, parents of NS and CM had always been aware of their sons' illness whereas the remaining parents had become less aware of asthmatic episodes.

Q5) LA and NJ were generally happier and were more willing to participate in games. LA, NJ and FM used less oral medication at the end of the study and LA, SA, NJ, FM and NS became less reliant on fenoterol inhaler. Only FM reported a decrease in absenteeism from school.

Summary

All the subjects experienced fewer asthmatic attacks and were more active by the end of the trial period. Five of the six subjects used less aerosol medication while four reduced their intake of oral medication. It is noteable that LA no longer required oral prednisone by the end of the trial period.

5.2.2.Questionnaire to control group

This questionnaire was completed at the end of the trial period and further questions were asked telephonically. The responses are discussed below.

Q1) Three subjects' asthma (SB, WF, FI) remained the same and three subjects' asthma improved (RA, JB, BF). However, only BF showed objective improvement in EIA during the trial period.

During the following three months WF's asthma improved and BF's asthma stopped improving but did not deteriorate.

Q2) Parents of four subjects (RA, JB, BF and WF) felt that their sons had an improved exercise tolerance at the end of the study but only BF showing objective evidence thereof.

Q3) Three subjects began new activities during the trial period. This reflected their desire to exercise but did not lead to an improvement in their vO_2 max.

Q4) Three subjects (SB, WF and FI) became more aware of their condition. BF had always been aware and JB became less aware (because he had not had an attack for several months).

Q5) Two groups of parents (of WF and FI) became more aware of asthma as a chronic illness while three (of RA, JB and BF) had always been aware of this.

Q6) Three subjects enjoyed treadmill running (SB, BF and WF).

Q7 & 8) The subjects and their parents were aware that they were part of the 'controls' and were still keen to participate in a training programme at the end of the study.

Q9) The answer to this question seemed to depend on domestic situations which were non-asthma related.

Only BF needed less medication (oral and inhaled) at the end of the study. WF required more medication while this remained unchanged in the remainder of the controls.

A noteable point is that all the parents and the subjects in the control group indicated that they were willing to participate in an exercise programme.

6.Daily diaries (table 15)

During September it appears that the control group was more symptomatic than the exercise group despite the worse EIA in the latter group.

However, the medication frequency differed: RA in the control group used the most amount of fenoterol aerosol; this was associated with low symptom scores for the month. Relatively high scores were obtained for the other subjects despite a wide range of fenoterol useage. In the exercise group, NJ was the worst and required the most medication. This was associated with the worst symptom scores.

Inter-group comparison of the symptom scores and medication leads one to think that the low symptom scores were due to regular aerosol useage. The low activity score confirms that the exercise group was more active than the controls. This could be due to the training programme or relatively good clinical status of the subjects or both.

Both groups indicated that they were relatively happy during the month. The subjects with the poorer scores (NJ and RA) had the worser clinical asthma during the month.

The subjects completed the diaries at home and some required the help of their parents or siblings. The poor compliance was similar in both groups. In retrospect it would have been better to have the children complete the diaries before a training session. During the trial period the subjects were regularly asked about the diary. Most indicated that they were completing it as requested, but I discovered the contrary at the end of the subsequent months (October and November). Most had forgotton

(despite saying that they had not !); some filled it in intermittently (whenever they remembered) and some lost it.

7.Medication prescribed at Red Cross War Memorial Children's Hospital

Clinical improvement was gauged by a reduction in prescription and this occurred in four subjects in the exercise group:

LA: all bronchodilator therapy was discontinued.

Stoppage of prednisone further indicates clinical improvement.

SA: fenoterol aerosol was stopped.

FM: cromoglycate was stopped and fenoterol was prescribed on a symptomatic basis.

NS: fenoterol was prescribed on a symptomatic basis.

In the questionnaire FM and NS stated that they had discontinued using fenoterol aerosol.

8.Allergy tests

Subject JB did not have any allergy testing but was prescribed nasal steroid aerosol (beclomethasone dipropionate, Beconase), indicating that he also had allergic rhinitis.

Two subjects were allergic to grass (LA and NJ) and outdoor training exposed them to this allergen but no adverse effects were noted.

CHAPTER VI

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

The training programme was a success as five of six subjects in the exercise group objectively improved their treadmill performance, maximal oxygen consumption and cardiovascular fitness. Improvement of clinical asthma was indicated by post-trial questionnaire responses and a reduction in prescribed medication in 4 sujects. Two of the four subjects showed improved EIA. These findings do not show causality between improved fitness and reduced EIA, but do show that severity of EIA is a non-specific indicator of clinical asthma. It appears that the increased fitness is associated with improved clinical asthma, but the sample size is too small for further speculation. A further confounding factor is the mean age difference between the groups. The mean age of the exercise group at the start of the study (13 $\pm$ 0.9 yrs) was greater than that of the control group (11.6 $\pm$ 1.2 yrs). The possibility of the exercise group 'outgrowing' their asthma more than the control group cannot be discounted. The reduced prescription of medication and the subjective improvement of the exercise group may reflect this. However, one could argue whether the exercise programme facilitated the improvement in the exercise group. These questions can only be answered by conducting age-specific exercise programmes which were out of the range of this study.

The above results are contrasted with the control group who did not show improvement in any of these factors.

The literature review discussed reports of blood lactate concentration and lactate turnpoint being relative to age, rather than body weight or working muscle mass. These parameters did not show changes in keeping with other measurements of improved

fitness (vO_2 max, maximal treadmill speed reached and heart rate at submaximal speed). The characterization of the role of glycolysis in exercise in pre-adolescents is a pre-requisite for better interpretation of these results. Future research should also include longitudinal studies to determine age related changes in the role of glycolysis in exercise as children mature. It is also unknown how exercise training modifies these factors in children.

The initial subject bias did not adversely affect the study as much as was initially thought. There was an improvement in clinical asthma in more subjects in the trained group than the controls despite the former group having more severe EIA. Inter- and intra- subject comparison would be made much easier if similar lung function baseline values had been present.

Future research should include the following :

1) Larger sample sizes.

2) Minimal inter-group differences in age, anthropometry and severity of asthma.

3) Equal attention given to the control and exercise groups.

4) Medication should be standardized as far as possible.

5) Psychological testing would add another dimension to the study and would place more confidence on the questionnaire responses which indicate unanimous support of an exercise programme.

The small sample size was sufficient to show statistically significant improvements in fitness (calculated with n5%). However, the variance associated with post-exercise lung function measurements does not allow confident interpretation of these

results. Exercise is one of many stimuli for bronchoconstriction and EIA should not be seen as a separate entity. Controversy still exists as to whether the initiating stimulus is heat or water loss or both from the respiratory tract. Ventilation rate during exercise determines the magnitude of the initiating stimulus and a logical way of reducing the stimulus is, through exercise training, to reduce the ventilation rate for a given workload. This however, was not shown in this study. Further investigation is needed into the initiating stimulus for EIA before interaction of the abovementioned factors can be more fully appreciated.

Despite having found improved clinical asthma in the exercise group, no direct causal relationship between improved cardio-respiratory fitness and reduced EIA has been established.

A causal relationship may apply for mild asthmatics who find it easier to train. The subsequent reduction in respiratory effort for a given workload represents a lesser stimulus for broncho-constriction , resulting in reduced EIA (Bundgaard et al, 1981).

Moderately severe asthmatics (this study) were able to improve their cardiovascular fitness but this did not diminish the maximal post-exercise falls in PEFR, FEV1 and MMEF. Conversely, asthmatics are only able to train effectively if their clinical asthma is under control. Since EIA appears to be an indicator of the severity of clinical asthma (Balfour-Lynn, Tooley and Godfrey, 1981), it follows that asthmatics who are able to train should have relatively improved EIA.

The sports-orientated clinican should be able to confidently advise asthmatic patients on an exercise programme provided that

the clinical asthma is well controlled. An exercise programme will also benefit patients who do not participate in regular sports as improved fitness will result in reduced cardiovascular effort for tasks requiring submaximal effort. The results of this study suggest that asthmatics who show improved fitness should also enjoy improved clinical asthma and reduced medication requirements.

Paediatricians should encourage asthmatic pre-adolescents to be physically active as these children should be living as 'normal' a lifestyle as possible. This will benefit especially children with mild airways obstruction and those who will 'outgrow' their asthma. It has yet to be determined whether control of clinical asthma or exercise training or both modifies the phenomenon of 'outgrowing of asthma'.

Exercise physiologists should be confident that asthmatic subjects will produce treadmill performances similar to that attained by normal subjects of similar fitness. The use of effective prophylactic medication before a maximal test ensures that bronchoconstriction does not prematurely terminate the test. The omission of pre-exercise medication will result in a symptom-limited performance, thus giving an indication of the severity of EIA rather than an assessment of the subject's level of fitness.

APPENDIX I

THE QUESTIONNAIRES

APPENDIX I

1) The following questionnaire was posted to all parents of the subjects before the trial period.

1. Why did you allow your son to participate in the study ?

   i) We want his asthma to improve.
   ii) He likes physical exercise.
   iii) We would like him to do more physical exercise than before.
   iv) Because we have no objections.
   v) other.

2. Has your son participated in any other study/trial before ?

3. How long has your son had asthma ?

   i) since a baby.
   i) more than 5 yrs.
   iii) between 2 and 5 yrs.
   iv) less than 2 yrs.
   v) other.

4. Over the past year his asthma has been

   i) improving.
   ii) worsening.
   iii) the same.
   iv) varies according to the season.
   v) variable and unpredictable.

5. How many days has your son been absent from school last year ?

6. On average how many times does your son get a cold/flu/chest problems a year ?

7. How would you compare your son's physical activity with that of your other children ?

   i) no other children.
   ii) more.
   iii) about the same.
   iv) less.
   v) don't know.
   vi) details.....

8.How would you compare your son's physical activity with that of his friends ?

i) more.
ii) about the same.
iii) less.
iv) don't know.

9. Does your son play regular sport at school ?

10. If yes, give details....

11. Is your son's physical activity limited at school or at home because of

i) advice of teacher.
ii) advice of doctor.
iii) decision of parents.
iv) he does not want to.
v) afraid of getting asthma.
vi) other....

12. Is your son a member of a sports team ?
If yes, give details....

13. Does your son take part in athletics ?
If yes, give details....

14. Does anyone else in the family play sports regularly ?
If yes, give details....

15. Does your son participate in recreational activities that involve physical exercise.

i) Bicycling.
ii) swims.
iii) other... (scouts)

16. If he is not active enough, what are the reasons ?

i) afraid of getting asthma
ii) not interested.
iii) no facilities.
iv) other interests.
v) I don't know.
vi) other...

17. Has your son been admitted to hospital for an asthma attack during the past 2 years ?

If yes, explain....

18. Mark off the statements which you think is correct.

i) Physical activity is important for one's health.
ii) Physical activity can help improve some illnesses.
iii) Physical activity is important to control one's weight.
iv) Physical activity is not needed by all.
v) It is more important for children to be fit than adults.
vi) Adults don't need to be fit.

19. As parents

i) We are reasonably fit.
ii) we don't have time to get fit.
iii) we don't have the necessary facilities.
iv) we make a point of doing regular exercise.
v) It is not important for us to be fit.
vi) we are too old to become fit.
vii) other....(no response)

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2) The questionnaire sent to parents of the exercise group after the training programme :

	YES	NO	don't know
1) SINCE THE TRAINING PROGRAMME HAVE YOU NOTICED :			
improvement in asthma			
less frequent attacks			
increased physical activity			
no difference in asthma			

2) HAS YOUR SON STARTED ANY NEW PHYSICAL ACTIVITIES SINCE THE TRAINING PROGRAMME BEGAN ?

3) HAS YOUR SON'S ATTITUDE TO HIS ASTHMA CHANGED ?

i) More aware

ii) Always been aware

iii) Less aware

4) HAS YOUR ATTITUDE TO ASTHMA CHANGED ?

i) More aware

ii) Always aware

iii) less aware

5) HAS THERE BEEN ANY CHANGE IN YOUR SON'S :

i) mood ?

ii) need for medicines ?

iii) need for inhalers ?

iv) school attendance ?

3) Questionnaire posted to the parents of the control group after the trial period :

	SAME	IMPROVE	WORSE	don't know
1) HOW HAS YOUR SON'S ASTHMA BEEN:				
i) SEPT.-DEC. 1985 :				
ii) JAN.-MARCH 1986 :				

	SAME	BETTER	WORSE	DON'T KNOW
2) HOW HAS YOUR SON'S ASTHMA BEEN AFTER EXERCISE ?				

3) HAS YOUR SON STARTED ANY NEW PHYSICAL ACTIVITIES SINCE SEPT. 1985 ?

4) HAS YOUR SON'S ATTITUDE TO HIS ASTHMA CHANGED ?

i) More aware of asthma as a chronic illness.

ii) Always been aware.

ii) less aware.

5) HAS YOUR ATTITUDE TO ASTHMA CHANGED ?

i) More aware.

ii) Always aware.

iii) less aware.

6) DID RUNNING ON THE TREADMILL AFFECT YOUR SON'S ATTITUDE TO EXERCISE ?

7) WOULD YOU HAVE LIKED TO PARTICIPATE IN THE EXERCISE PROGRAM ?

8) IF YOU HAD THE OPPORTUNITY TO PARTICIPATE IN AN EXERCISE PROGRAM, WOULD YOU LIKE TO JOIN ?

9) HAS THERE BEEN ANY CHANGE IN YOUR SON'S:

i) mood ?

ii) need for medicines ?

iii) need for inhaler (Berotec) ?

iv) school attendance ?

APPENDIX II

ANALYTICAL METHODS

APPENDIX II

BLOOD LACTATE LEVELS

1.2 ml of blood was placed in a previously weighed plastic test tube containing 2 ml of ice-cold 0.6 N perchloric acid (PCA). The tube was shaken thouroughly, weighed and placed in a refridgerator. Within two hours the same test tube was placed in a centrifuge at 2000 RPM for 15 minutes. The supernatant was decanted off and stored in a sealed test tube in a freezer ($4^{o}C$) until the assays were performed.

ASSAY METHOD

Cuvettes were made up using 3 blanks and 2 standards as follows :

(All volumes in ml)	STD	BLANK	TEST
Hydralazine buffer	1.0	1.0	1.0
NAD	0.1	0.1	0.1
PCA	-	0.1	-
LDH	0.01	0.01	0.01
Supernatant	-	-	0.1
Standard (Std)	0.1	-	-

The solutions were mixed (vortex mixer Fissons BP 931263) and allowed to equilibrate to room temperature for 30 mins.

The absorbtion at 340 nm was then read using a spectrophotometer (Beckman Instruments, Spectrophotometer Model 35), zeroed against distilled water.

APPENDIX II cont..

The following mathematical formula was used :

$$\frac{\text{Total vol in cuvette}}{\text{Vol of supernant}} \times \frac{\text{Vol of PCA + Vol blood}}{\text{Vol blood}} \times \frac{1}{6.22}$$

6.22= molar extinction coefficient of NADH

Product is expressed in mmol ml^{-1}.

APPENDIX III

CALCULATIONS AND COMPUTER PROGRAMMES

CALCULATIONS

The calculation for the determination of percentage body fat (Durnin and Rahaman, 1967) is as follows:

BODY DENSITY (D) = 1.1533 - (0.0643 x s)

s = log (sum of skinfolds [subscapular + suprailiac + biceps + triceps] mm)

% BODY FAT = (100 x [4.95/D])

Computer programme written by Dr Mike Power for the calculation of 'beta'.
'Beta.prg' was written specifically for 'Database III' (Ashton Tate).

```
Note/*  This program calculates "N5%" and Beta given the numbers, means and
Note/*  standard deviations of a set of data.
Note/*  N5% is an (optimistic) estimate of the number of subjects required in
Note/*  EACH of the two groups for a t test to reach 5% significance
Note/*  Beta is the type II error
Note/*
Note/*  VARIABLES:
Note/*        Variable              Name (ie Lotus Lable) of the variable
Note/*        N_CTL, N_TST          Numbers in Control and Test Groups
Note/*        Mean_CTL, Mean_TST    Means in  Control and Test Groups
Note/*        SD_CTL, SD_TST        Standard Deviations in Control and Test Groups
Note/*        Beta                  Type II error for Alpha = 5%
Note/*        N_5_PCT               Estimate of the number in EACH group required
Note/*                                   for p=5% given the 2 means and Std Devs.
Note/*                                   NB  this is an UNDERestimate; for full
Note/*                                   details see Colton, Statistics in
Note/*                                   Medicine
Note/*
Note/*  FILES:
Note/*        STATS.dbf             Contains the statistics
Note/*                              NB Must have above the fields
Note/*        ONETAIL.dbf           Contains the areas in ONE TAIL of the normal
Note/*                                   curve; Taken from Colton, Table A1
Note/*        Z.ndx                 Index for ONETAIL
CLEAR
set default to b
set console on
set talk off
set echo off
select 1
use onetail index z
select 2
use stats
go top
clear
r1=0
DO WHILE .not. eof()
   clear
   r1=r1+1
   @ 1,1 say 'record # '
   ?? r1
   ? variable
N=2*(1.96*SD_ALL/(MEAN_CTL-MEAN_TST))**2
   n=int(n+0.5)
   if n > 99999999
      n = 99999999
      endif
   IF MEAN_ctl < mean_TST
      V1=MEAN_CTL
      V2=MEAN_TST
      S1=SD_CTL
      S2=SD_TST
      N1=N_CTL
      N2=N_TST
      ELSE
```

'Beta.prg' continued...

```
            V1=MEAN_TST
            V2=MEAN_CTL
            S1=SD_TST
            S2=SD_CTL
            N1=N_TST
            N2=N_CTL
         ENDIF
      X=1.96*S1/SQRT(N1)+V1
      T=1
      Z1=(V2-X)*SQRT(N2)/S2
      IF Z1 < 0
         Z1=-Z1
         T=-1
      ENDIF
      IF Z1 > 2.99
         Z1 = 2.99
      ENDIF
      z1=ROUND(Z1,2)
      select 1
      seek z1
      if eof()
         set console on
         set debug on
         @ 1,1 say 'funny Z = '
         ?? z1
         display memory to print
         display next 1 to print
         select 2
         display next 1 to print
         cancel
         endif
      select 2
      replace n_5_pct with n
      b1=a->AREA
      IF T < 0
         b1=1-b1
         ENDIF
      replace beta with b1
      SKIP
   ENDDO
set console on
LIST OFF VARIABLE,N_5_PCT,BETA
CLEAR
@ 1,1 SAY 'DONE'
```

Computer programme written by Dr Mike Power for the calculation of the 95% confidence limits. 'Conlimit.prg was written for 'Database III' (Ashton Tate).

```
Note/*        program to calculate 95% confidence limits OF MEANS
Note/*
Note/*  VARIABLES:
Note/*        Variable              Name (ie Lotus Lable) of the variable
Note/*        N_ALL, N_CTL, N_TST   Numbers in All, Control and Test Groups
Note/*        Mean_ALL, Mean_CTL,   Mean_TST
Note/*                              Means in  All, Control and Test Groups
Note/*        SD_ALL, SD_CTL, SD_TST
Note/*                              Standard Deviations in All, Control and Test
Note/*                                   Groups
Note/*        MAF, MCF, MTF         Lower bound (Floor) of 95% confidence limit
Note/*        MAC, MCC, MTC         Upper bound (Ceiling) of 95% confidence limit
Note/*
Note/*  FILES:
Note/*        STATS.dbf             Contains the statistics
Note/*                                   NB Must have above the fields
Note/*        T95TAB.dbf            Table of Significance limits of the t
Note/*                                   distribution from Ciba-Geigy Scientific
Note/*                                   Tables 7th edition pp 32-35
Note/*        N.ndx                 Index for above table
Note/*
clear
set echo off
set talk off
set default to b
select 1
use t95tab index n
select 2
use stats
go top
r1=0
do while .not. eof()
  clear
  r1=r1+1
  @1,1 say 'record '
  ? r1
  @3,1 say variable
  na=n_all
  if na<1
     na=1
     endif
  if na>200
     na=200
     endif
```

'Conlimit.prg' cont...

```
   nc=n_ctl
   if nc<1
      nc=1
      endif
   if nc>200
      nc=200
      endif
   nt=n_tst
   if nt<1
      nt=1
      endif
   if nt>200
      nt=200
      endif
   select 1
   seek na
   ta=t95
   seek nc
   tc=t95
   seek nt
   tt=t95
   select 2
   replace maf with (mean_all - ta*sd_all/sqrt(n_all))
   replace mac with (mean_all + ta*sd_all/sqrt(n_all))
   replace mcf with (mean_ctl - tc*sd_ctl/sqrt(n_ctl))
   replace mcc with (mean_ctl + tc*sd_ctl/sqrt(n_ctl))
   replace mtf with (mean_tst - tt*sd_tst/sqrt(n_tst))
   replace mtc with (mean_tst + tt*sd_tst/sqrt(n_tst))
   skip
enddo
@ 15,15 say 'd o n e'
```

APPENDIX IV

THE HOME EXERCISE PROGRAMME

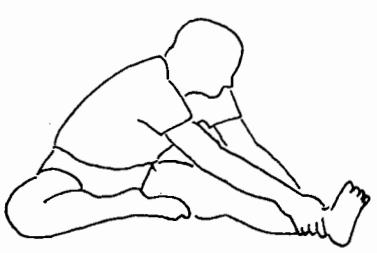
THE HOME EXERCISE PROGRAMME

I devised a home exercise programme for the exercise group in case they were unable to attend the sessions at Red Cross Childrens' Hospital. It was not intended to replace the training sessions at the Hospital, but was a guideline for the children to keep active at home :

This is best done with friends, or brothers or sisters in an open space such as a nearby park. You should do the exercises for at least a half an hour. If you think that you cannot get to the Red Cross Hospital for a whole week, try to do the exercises at least every second day.

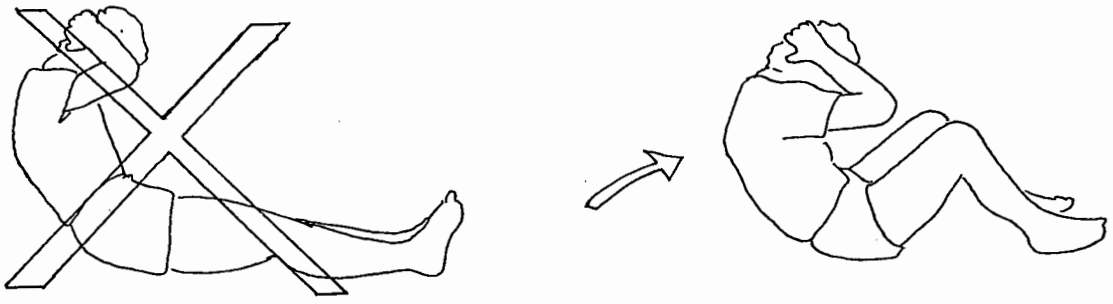
1) Take your medicines regularly, especially the Berotec Inhaler and Lomudal Spinhaler before you exercise.
2) JOG slowly for 5 minutes to warm up: on the spot, around the park or down the road.
3) STRETCH the back of your thigh :

-count to 60 while stretching each leg.

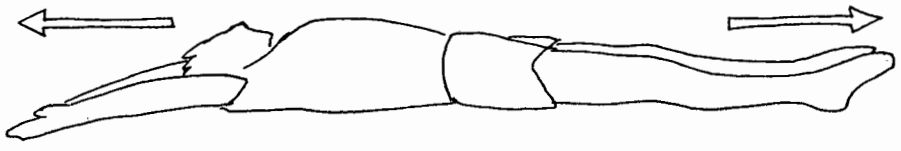


3) STRETCH the front of your thighs :

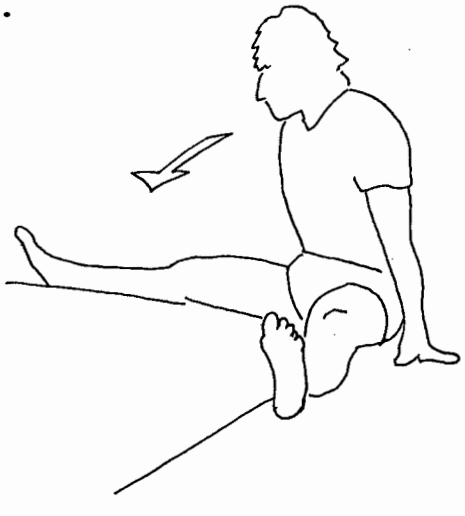
-count to 60 while doing this stretch.



4) Do 10 SIT-UPS with your knees bent. Hook your feet under a pole, or have a fiend sitting on your feet. Do this slowly and smoothly.



5) LAY FLAT on your back, extend your arms above your head and keep your feet together. Reach in opposite directions with your hands and feet till you feel your tummy muscles stretch. Count to 10 slowly, then relax. Do this a few times.

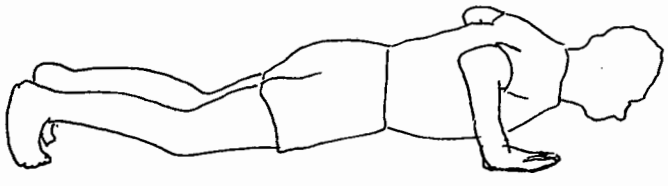


6) JOG slowly for 5 minutes.
   Do a few short sprints (40-50 m each).
   SKIP for 2-3 minutes.

7) STRETCH your GROIN and HIPS : Sit at the corner of a mat if possible, so that your legs form a right angle. Place your hands behind you and lean forward. Count to 60 slowly.

8) AIR SOCCER : Try to keep a soccer or tennis ball in the air by kicking with your feet, knees or thighs, or by heading the ball. This is very difficult to do, but you will improve with practice

9) PUSH-UPS : Keep your body as stiff as possible. Do 10.



10) Play SOCCER or go CYCLING with your friends if possible. Do this for as long as you like.

The main thing is to keep fit by being active as long as you enjoy doing it. Try to do most of the exercises: at least try to work up at bit of a sweat !

Take your pulse afte running : try to exercise till your heart rate is about 140-150 beats per minute.

GOOD LUCK !

APPENDIX V

THE DAILY DIARY

NAME DATE ---------- 19-----	DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14
(1) Good night	0														
NIGHT Slept well but slightly wheezy.....	1														
WHEEZE Woken x 2-3 because of wheeze	2														
Bad night, awake most of the time	3														
(2) None	0														
NIGHT Little	1														
COUGH Moderately bad	2														
Severe	3														
(3) None	0														
DAY Little	1														
WHEEZE Moderately bad	2														
Severe	3														
(4) Quite normal	0														
ACTIVITY Could run short distance	1														
DURING Limited to walking	2														
DAY Off work/school or indoors due to chest symptoms	3														
(5) Dose of any drugs being taken, record number of tablets or puffs daily. 1. Tablets 2. Inhaler 3. Lomudal															
(6) (Only if there is anything unusual to COMMENTS report, e.g. a cold).															
(7) SMILE CHART 															
(8) WEATHER TODAY															

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