University of Alberta

Immune Modulation Imagery as an Adjunct Treatment for Asthma

by

Keith E. Zukiwski 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled "Immune Modulation Imagery as an Adjunct Treatment for Asthma" submitted by Keith E. Zukiwski in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Counselling Psychology.

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DEDICATION

I dedicate this thesis to my mother, Lydia Zukiwski. She helped me appreciate the value of a university education, and has supported me through every step with patience, encouragement, and optimism.

ABSTRACT

Mental imagery as an adjunct treatment for asthma was investigated in this study. An 8-week single-blinded, two-group study was conducted to examine the efficacy of disease specific imagery in reducing airway obstruction. Twenty-six non-smoking adults (19 to 64 years old) with moderate to severe asthma on stable regimens of inhaled corticosteroids were randomly assigned to receive training in either immune modulation imagery or relaxation imagery. Six men and 10 women with a mean age of 46 (range 24-64) completed the study. The treatment group (n = 9) practiced daily visualization of imagery representing modulation of inflammatory cell activity related to airway inflammation. A comparison group (n = 6) practiced relaxation imagery to control for treatment factors other than imagery content such as relaxation, imagery practice, and expectancy. Primary efficacy measures included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF) obtained by spirometry before and after administration of short-acting bronchodilator. The treatment group demonstrated greater improvements in FEV_1, FVC, and PEF, before and after bronchodilator, than the relaxation group. On all primary outcome measures, the treatment group had improvements in lung function (between 6 to 10%) that were greater than the comparison group (unchanged or decreased lung function). The between group difference on one measure (post-bronchodilator PEF) was statistically significant ($p = .036$). Secondary efficacy data from daily asthma diaries indicated trends of decreasing PEF and decreasing use of short acting bronchodilator medication. In the treatment group, 7 of the 9 participants had clinically significant improvements in lung function

compared to none in the relaxation group. Anecdotal reports included voluntary control of symptom exacerbations, decreased feeling of panic when without reliever medication, increased feeling of control over asthma, and decreased subjective psychological distress. The findings suggest that immune modulation imagery had the effect of decreasing airway inflammation, resulting in reduced airway obstruction as measured by spirometry. Thus, immune modulation imagery may be a valuable adjunct treatment that provides asthma patients with increased control over their disease.

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CHAPTER 1: INTRODUCTION

Despite the limitations of conventional medicine, physicians largely ignore psychological treatments such as imagery, relaxation, and hypnosis. Of psychological approaches, one of the most exciting is mental imagery with its potential as a tool to target underlying immunologic processes of diseases such as asthma. While significant strides have been made in the pharmacological treatment of asthma, many patients could benefit from additional adjunct treatments that may improve quality of life by decreasing symptoms, improving lung function, and even reducing medication usage.

Asthma is a complex and heterogeneous disease that encompasses a wide spectrum of conditions. It is a disease of reversible obstructive airways, bronchial hyperresponsiveness, and eosinophilic desquamative inflammation (Boulet et al., 2001). Individuals with asthma experience a variety of symptoms, including dyspnea, wheezing, cough, chest tightness, and sputum production. Occasionally fatal, asthma is a very important disease that can severely impair quality of life and burden individuals and health systems with expensive treatments. It is a chronic condition that may require life long treatment with medications that decrease airway inflammation and relieve symptoms by reducing bronchoconstriction.

While beta$_2$-agonist bronchodilators and corticosteroids are effective therapies they are not free of serious side effects. Bone demineralization may occur with both oral (Baltzan, Suissa, & Bauer, 1999) and inhaled corticosteroids (Wong et al., 2000). Prolonged use of inhaled bronchodilators has been associated with increased bronchial hyperresponsiveness to allergen and decreased baseline lung function (Taylor, Sears, & Cockroft, 1996), and increased mortality (Beasley, Pearce, Crane, & Burgess, 1999).

Psychophysiological Treatments

Despite prolonged treatment with inhaled or oral corticosteroids, many individuals with asthma experience symptoms daily and are limited in work and recreational activities. As with other chronic or life threatening illnesses patients often seek out psychophysiological treatments such as mental imagery or relaxation therapy in conjunction with allopathic treatments (Eisenberg et al., 1993). Modern medicine

appears to be slowly moving towards gaining a better understanding and willingness to apply mental imagery techniques. Imagery has been an integral component of native healing practices for centuries (Achterberg, 1985; Money, 1997).

The use of imagery incorporating modern knowledge of the immune system began in the 1970's with an anecdotal report of its use with cancer patients (Simonton, Mathews-Simonton, & Creighton, 1978). The treatment approach involves imagining desired physiological changes while in a relaxed and focused state. It has been widely used in clinical practice by psychologists and by medical professionals. Controlled experiments with normal subjects provided evidence that mental imagery may be used to intentionally alter the activity and numbers of various leucocytes. A series of studies demonstrated altered neutrophil adhesion immediately following practice of immune specific imagery (e.g., Hall, Minnes, Tosi, & Olness, 1992; Hall, Papas, Tosi, & Olness, 1996).

Before the inflammatory component of asthma was well understood, asthma was commonly considered a psychosomatic disorder with bronchospasm as the primary feature. Psychological treatments focused on the association between psychological factors of anxiety and tension and increased asthma symptoms (Lask, 1991). Relaxation training (Lehrer, Hochron, McCann, Swartzman, & Reba, 1986), hypnosis (Brown & Fromm, 1988), behavioral management (King, 1980), and psychotherapy (Meany, McNamara, Burks, Berger, & Sayle, 1988) were evaluated as potential treatments for asthma. Although the inflammatory component of asthma is now well understood, there have been no controlled studies of psychological treatments designed to directly modulate the components of airway inflammation.

My interest in this area of research developed from an extensive review of the literature in the areas of psychoneuroimmunology, imagery, and hypnosis. Psychoneuroimmunology research has clearly established the mind-body connection by documenting the interactions between the nervous system, endocrine system, and immune system (Ader, Cohen, & Felten, 1995; Bateman, Singh, Kral, & Solomon, 1989; Cohen, Ader, & Felton, 1994). Controlled studies on hypnosis have documented remarkable examples of physiological changes following hypnotic suggestions, including: wart

regression (Spanos, Williams, & Gwynn, 1990), altered hypersensitivity reactions (Smith, McKenzie, Marmer, & Steel, 1985), and blister formation (Johnson & Barber, 1976). This evidence suggests that the "mind" can create rapid and controllable physiological changes in the body. Other research has shown that mental imagery has potential as a tool for targeting the activity and/or production of specific leukocytes (Hall et al., 1996) or other components of the immune system such as immunoglobulins (Rider & Weldin, 1990).

Rossi (1993) speculated that mental imagery techniques utilized to alter neutrophil adhesion might be adapted to decrease eosinophil migration into the airways of asthma patients. Asthma meets the criteria of a useful disease model for investigating psychological techniques of immunomodulation; the molecular-genetic and information substances-receptor pathways involved in asthma are extensively documented, reliable biochemical assay methods are available, and presence of disease severity and its severity is easily observed and measured (Rossi).

Preliminary study. In my master's thesis (Zukiwski, 1996), I embarked on a program of research to develop and test a psychological treatment for asthma that targeted multiple facets of asthma pathophysiology. With the goal of later conducting a controlled trial, I conducted a preliminary uncontrolled study (Zukiwski, 1996). The study had two stated goals: (a) investigate the efficacy of imagery as an adjunct treatment for asthma, and (b) refine a treatment protocol for use in a future controlled study. I developed a treatment protocol incorporating current research on asthma immunology and pathophysiology and tested it in several case studies.

The treatment protocol created for the pilot study featured education about the physiological changes associated with improvements in functioning of the lungs. The subjects created their own imagery to represent these changes, which included a reduction of inflammation of the airways. Utilizing a single-subject design, 5 adults with asthma participated in 8 weeks of training in imagery. One subject was withdrawn from the study due to a change in asthma medication during the study and an inability to attend 4 out of 8 treatment sessions. A second subject was withdrawn from the analysis due to repeated illness, including bronchitis, and associated asthma exacerbation.

The results of the pilot study were that some measure of improvement compared to baseline occurred in all three cases. Increases in morning peak expiratory flow (PEF) were observed in Cases 1 and 3. A significant decrease in residual volume (RV) occurred in Case 2. In Case 3, significant increases were observed in post-bronchodilator forced expiratory volume in one second (FEV_1) and mean forced expiratory flow between 25% and 75% of the expired vital capacity ($FEF_{25-75\%}$). Finally, improvement in daily self-reported symptoms occurred in all 3 cases.

The results of the pilot study, though anecdotal, suggest that further controlled research on this treatment approach is warranted. Building on this initial research, the current study is designed to examine the effectiveness of the treatment protocol through a more rigorous controlled experiment.

I am approaching asthma from the perspective of a psychologist. Evidence of immunomodulation following imagery practice has been documented in normal populations, but is largely anecdotal in clinical populations. It is important to be skeptical of anecdotal evidence and conduct controlled clinical trials to determine if imagery treatments are truly beneficial. If so, they may be important adjunct treatments that improve the quality of life of asthma patients. It is unlikely that asthma patients will be placed at any additional risk with the use of imagery as an adjunct treatment as there are no known negative side effects with this treatment. If physicians could reduce medication use because of decreased airway inflammation and improved lung function, financial costs and medication side effects may be reduced.

This study will address the following questions:

1. Does regular practice of relaxation-assisted mental imagery representing modulation of airway inflammation increase lung function in adults with asthma?
2. Treatment with immune specific imagery involves many components, such as education, daily practice of relaxation, the process of creating and practicing mental imagery, and a therapeutic relationship with the researcher or research assistants. Is immune specific imagery the causal factor of improvements of lung function, or is another component, such as relaxation, the primary causal factor?

Hypothesis

This study will examine one primary hypothesis: ***Adults with moderate asthma who are trained in, and practice, using relaxation-assisted imagery representing desirable functional and cellular changes in the lungs will show improvement in lung function more than those who receive the same degree of education about asthma, but are trained in, and practice, using relaxation-assisted "calm scene" imagery.***

Overview

This hypothesis is based on data that has been published in the literature and my own preliminary data obtained during my master's thesis research. I approached this task by training volunteers in the use of imagery designed to modulate inflammatory components of asthma (e.g., decreased eosinophil activation and adhesion, mucus production, and airway smooth muscle hyperreactivity). Factors that are involved in treatment such as education, researcher effects, relaxation training, and imagery practice were controlled through the use of a referent group that received an identical treatment with the exception of type of mental imagery. The referent group was trained in the use of "calm scene" imagery that is consistent with relaxation training. For example, participants in the referent group imagined themselves at a beach or other setting they chose that would help them feel calm and relaxed. Treatment effectiveness was assessed with pre- and post-treatment spirometry and daily measures of peak expiratory flow and symptoms.

It is important to highlight that this study compared two psychological treatment strategies that are utilized in clinical practice and are considered valid treatment options in the health psychology community. In addition, all participants were required to be on a stable treatment regimen that included inhaled corticosteroids. Thus, this study recorded changes in lung function that occurred over and above accepted medical treatment and compared these changes for two psychological treatments to determine if the difference was statistically significant.

This thesis will begin with a literature review to provide the background for this study. The importance of asthma will be illustrated by a discussion of pathophysiology and epidemiology. A basic understanding of the inflammatory components of asthma is

crucial to understand the rationale for the treatment protocol. Clinicians applying this treatment require a working knowledge of the immune system to assist patients in developing imagery that correctly represents the desired immune changes. A brief review of the prevalence and costs of asthma will illustrate that despite excellent and constantly advancing allopathic treatment, the personal and financial costs of asthma continue to rise in developed nations. A rudimentary description of lung physiology, pulmonary function assessment, and asthma diagnosis will assist the reader in understanding the assessment procedures, data, and clinical relevance of the results. A review of current pharmacological treatments and their side effects is relevant to the rationale behind the research protocol and an appreciation of the personal costs to the asthma patient. Finally, I hope that an overview of immunomodulation research and psychological treatments for cancer, HIV/AIDS, and asthma will provide a context for the treatment examined in this study.

CHAPTER 2: REVIEW OF THE LITERATURE

What is Asthma and Why is it a Concern

Definition

Asthma is a disorder of the airways "characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and a variable degree of hyperresponsiveness of airways to endogenous or exogenous stimuli" (Boulet, Becker, Bérubé, & Beveridge, 1999, p. 2). Airway inflammation appears to be a central feature in all manifestations of asthma, ranging from mild to severe. The key inflammatory cells involved in asthma are eosinophils, mast cells, and T lymphocytes. Asthma involves narrowing of the airways as a result of contraction of the airway smooth muscles that encircle the trachea and bronchi, thickening of the airway wall from edema and infiltration by cells of the immune system, hyperplasia (an increase in the numbers) and hypertrophy (enlargement) of smooth muscle cells, and blockage of the airways from accumulated mucus, secretions, and cellular debris (Murray, 1995).

Epidemiology

An estimated 130 million people have asthma worldwide (Sears, 1997). With a prevalence of 11%, asthma is the second most common chronic medical condition among Canadian children, second only to non-food allergies (14%) (Statistics Canada, 1998).

English speaking western countries have the highest prevalences for asthma symptoms. A recent epidemiological study encompassing 56 countries, found that the United Kingdom, New Zealand, Australia, Ireland, and Canada had the highest prevalence of asthma symptoms in children aged 13-14 years (Worldwide variation, 1998). Children with asthma have 2.8 times greater total health care expenditures than children without asthma (Lozano, Sullivan, Smith, & Weiss, 1999). Cost to treat adults with moderately severe airway obstruction using a combination of inhaled corticosteroids and inhaled beta$_2$-agonists was estimated at $572 per year (Rutten-van Molken, van Doorslaer, Jansen, Kerstjens, & Rutten, 1995).

Epidemiological studies have revealed that a variety of host and environmental factors act as determinants of asthma. Beklake and Ernst (1997) describe primary factors,

which affect the incidence of asthma, and secondary factors, which trigger asthma symptoms or increase asthma severity. Established primary determinants and risk factors include: genetic factors, family history of allergies, allergen responsiveness (atopy), occupational exposure to certain substances, community air pollution by allergen, and post-natal sustained exposure to indoor allergens. Established secondary determinants include: sustained post-natal exposure to indoor allergens, viral infections, pre- and post-natal environmental exposure to tobacco smoke in childhood, and changing lifestyles (such as westernized lifestyle, urban living, migration, and changes in residence). Determinants suspected as being both primary and secondary include: maternal history, racial/ethnic origin, vehicle exhaust pollution, diets, absent or short duration breast feeding, absence of certain infections in infancy, indoor dampness, gas cooking, carpeting, electric home heating, and poverty. While outdoor air pollutants are associated with asthma exacerbation, they have not been shown to cause asthma (Koenig, 1999). Peat and Janet (1999) advocated a proactive approach to addressing increasing prevalence rates. Areas with the most potential for intervention include limiting exposure to parental smoking and allergens, increasing intake of healthy dietary fatty acids, and promoting breast feeding (factors in breast milk help prevent allergic illness and respiratory infections). Numerous genetic factors are currently under study and offer promise as a future target of intervention (Anderson & Cookson, 1999; Holgate, 1999; Ober & Moffatt, 2000).

Exposure to allergens or irritants in the workplace may also be a causative factor in asthma. Of 86 asthma patients with occupationally or environmentally induced asthma referred to the University of South Florida Occupational and Environmental Medical Clinic, 11(24%) had asthma caused by workplace allergens and 54(63%) had asthma related to workplace irritants (Brooks, 1998). Asthma associated with exposure to irritants has two clinical presentations: sudden and not-so-sudden onsets (Brooks). With sudden onset, symptoms begin immediately or within 24 hours following brief massive exposure to a vapor, gas, or fume. Bronchial mucosal inflammation and airway hyperresponsiveness is related to airway damage from massive irritant exposure. The slower onset presentation follows a smaller exposure for more than 24 hours. Atopy

(allergen responsiveness) was evident in 88% of individuals with the not-so-sudden irritant-induced asthma. Atopy is a significant contributor to the development of not-so-sudden irritant-induced asthma.

Approximately 4% of patients die of asthma and most are elderly (Reed, 1999). Death is most often caused by respiratory infection or other complication resulting from irreversible lung disease or by cardiac disease associated with theophylline enhanced hypoxemia or cardiotoxic effects of adrenergic agonists (Torren & Lindholm, 1996).

Pathophysiology of Asthma

The imagery technique in this study requires both the therapist and patient/research participant to understand the disease process involved in asthma. Asthma is a complicated disease involving numerous pathophysiological changes in the airways of the lungs and at the immune system level. I will review the components of asthma that are relevant to developing a treatment protocol featuring images of desirable changes.

Atopy and Airway Inflammation

Allergic reactions frequently contribute to airway inflammation. Following exposure to an allergen to which an individual is sensitized, there is an immediate response (early asthmatic response) and frequently, but not always, a delayed response (late asthmatic response), each involving different immune cells (Figure 1).

Early asthmatic response. The early asthmatic response is largely the result of mast cells resident in the airways responding to the presence of allergens to which they are sensitized (Dolovich & Hargreave, 1992). When immunoglobulin E antibodies (IgE) on the surface of the mast cell binds specifically to an allergen, the cross-bridging of the IgE receptors triggers a cascade of intracellular events that lead to the release of histamine and other pharmacologically-active mediators. The effects of these mediators include contraction of airways smooth muscle and damage to the airway epithelium (Murray, 1995). Contraction of the airways smooth muscle causing bronchial obstruction develops rapidly with peak airflow obstruction occurring within 20 to 30 minutes (Horowitz & Busse, 1995). Leukotrienes released by mast cells in the early phase and by eosinophils

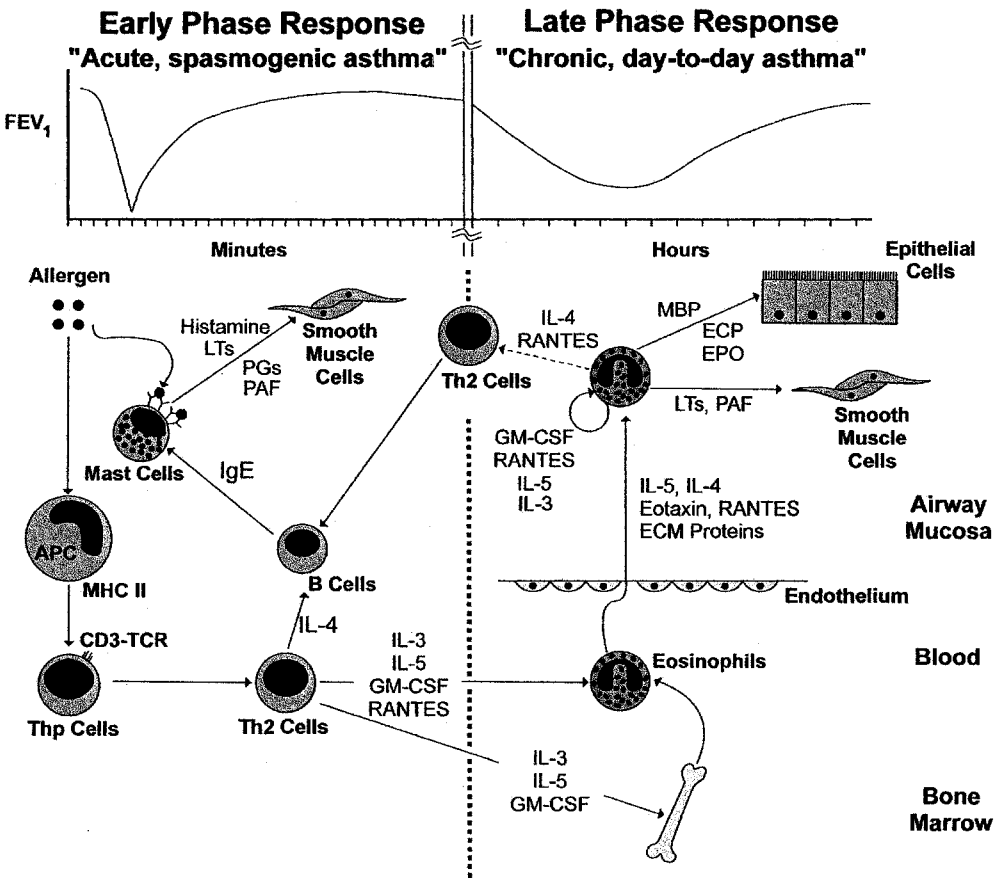

Figure 1. Immune and inflammatory mechanisms regulating the early and late phase asthmatic response. APC = antigen presenting cells; ECM = extracellular matrix proteins; ECP = eosinophil cationic protein; EPO = eosinophil peroxidase; FEV_1 = forced expiratory volume in 1 s; GM-CSF = granulocyte-macrophage colony-stimulating factor; Ig = immunoglobulin; IL = interleukin; MBP = major basic protein; MHC = major histocompatibility complex; PAF = platelet activating factor; PG = prostaglantin; Th = T helper cells; Thp = T helper precursor; TCR = T cell receptor. Scheme courtesy of Redwan Moqbel.

in the late phase are potent constrictors of airway smooth muscle and play an important role in the development and persistence of airway inflammation (Moqbel, 1999).

Allergic response may occur in the nose, sinuses, or in the lungs. Allergic rhinitis and asthma are frequently co-morbid conditions, and rhinitis is a risk factor for asthma (Leynaert, Bousquet, Neukirch, Liard, & Neukirch, 1999). Estelle & Simons (1999) propose the term "allergic rhinobronchitis" to refer to chronic inflammation throughout the upper and lower airways. Perennial rhinitis is strongly associated with asthma in atopic and non-atopic subjects (Leynaert et al.).

Respiratory illness may contribute to the development and exacerbation of asthma. Human Rhinovirus (HRV) infection has been shown to cause immunoglobulin isotype switching to immunoglobulin E (Rager et al., 1998), and up regulation of intercellular adhesion molecule-1 (ICAM-1) messenger RNA (Terajima et al., 1997).

Exposure to environmental allergens at home and at school is an important factor in atopic asthma. Lindfors, Hafe-Hamsten, Rietz, Wickman, & Nordvall (1999) found a dose-response relationship between cat exposure (animal exposure or allergen levels in dust) and sensitization to cat. The presence of environmental tobacco smoke (ETS) and dampness in the home increased the risk of sensitization. In this sample of children referred to a pediatric allergy clinic for evaluation for asthma, exposure to the combined risk factors of cat exposure, ETS and dampness, 80% exhibited IgE antibodies to cat. Only 9% of children exposed to none of these risk factors exhibited IgE antibodies to cat.

Late asthmatic response. Approximately 6 to 10 hours after exposure to allergen, a second phase of airflow obstruction can be observed (Horowitz & Busse, 1995). Mediators released during the early asthmatic response by the mast cells travel through the blood stream to recruit other leukocytes to the lung (Murray, 1995). When alerted by inflammatory mediators, circulating inflammatory cells such as eosinophils, and neutrophils become active, producing adhesion molecules on their surface. Inflammatory cells may also move additional adhesion molecules from inside the cell to its surface.

The inflammatory mediators also signal the expression of adhesion molecules on the surface of the endothelium (layer of cells that line the airways), regulating the adhesion and migration of the leukocytes (white blood cells) (Walker & Virchow, 1993).

Adhesion molecules allow the circulating eosinophils and other leukocytes to adhere to vascular endothelial cells. The cells roll along the surface of the blood vessel until they contact activated epithelial cells. After penetrating the endothelium through gaps between the endothelial cells created by mast cell mediators, the inflammatory cells migrate across the endothelium into the airway tissues where they then release their own mediators.

The eosinophil has been identified as a key leukocyte in the development of airway inflammation. Clinical severity of asthma and pulmonary function is correlated with levels of eosinophils and eosinophil cationic proteins in bronchoalveolar-lavage fluid (Bousquet et al., 1990). Eosinophil cytotoxic proteins cause epithelial cell damage, mucosal edema, airway inflammation, and contraction of airway smooth muscle (Murray, 1995). Cytotoxic (destroys or damages tissue cells) proteins released by the eosinophil are designed to kill metazoan parasites. But, in the case of asthma, they cause epithelial cell damage, mucosal edema, airway inflammation, and contraction of airway smooth muscle (Murray). The effect of these mediators on the airways can be observed as the second phase of airflow obstruction (late asthmatic response) (Horowitz & Busse, 1995).

T lymphocytes resident in the airways and others that are recruited to the airways by mast cell mediators contribute to the inflammatory process. T lymphocytes stimulate B cells to produce IgE antibodies, which may coat eosinophils and mast cells. IgE is involved in causing further stimulation of these cells in response to an allergen challenge. T lymphocytes also release mediators that recruit and activate other inflammatory cells (Horowitz & Busse, 1995).

Mucosal Lining

The mucosal lining of the nose and airways serves a protective function by trapping bacteria and debris. Goblet cells and submucosal glands produce mucus. In asthma, there is an increase in the number of goblet cells by metaplasia (Wanner, Salathé, & O'Riordan, 1996). The cilia move the mucus up the respiratory tract to the throat where it can be transported to the stomach. Sputum quantity, quality, and viscosity, as well as ciliary function and epithelial integrity, are factors that determine mucociliary

clearance (Wanner et al.). In asthma, there is increased production of mucus and thickening of mucus, which can form into "plugs" and block the airways.

In an extensive review of mucociliary clearance, Wanner et al. (1996) report: (a) in allergic subjects, exposure to allergen decreases mucociliary transport velocity and increases mucus hypersecretion; (b) leukocyte products, such as eosinophil cationic proteins, stimulate mucus secretion by goblet cells and submucosal glands; (c) various substances released during inflammation, such as eosinophil major basic protein, are related to inhibition of the ciliary activity; (d) subtle mucociliary impairment has been detected in patients with stable asthma; (e) during severe asthma exacerbation mucociliary clearance is impaired; and (f) impairment of mucociliary clearance in less severe and mild asthma occurs mainly in the central airways.

Epithelial Injury

Asthma is a progressive disease that may lead to irreversible lung obstruction in 80% of elderly patients (Reed, 1999). Airway remodeling brought about by eosinophilic inflammation is one of the causes of this loss of lung function. Many of the pathological changes to the airways, such as pseudo-thickening of the base membrane, disruption of the elastic fibers, and hypertrophy of the bronchial smooth muscles, may be irreversible (Goddard, Chanez, Redier, Bousquet, & Michel, 1994).

Epithelial injury occurs in asthma as a result of mediators released from inflammatory cells. Desquamation (peeling off) of epithelial cells enhances the access of mediators to the smooth muscle and exposed neurons increasing smooth muscle contraction (Murray, 1995). In asthma, the natural process of repairing the epithelium may be impaired. As a result there may be goblet cell metaplasia and an accumulation of fibrous scar tissue leading to thickened lamina reticularis and narrowing of the airways (Rennard, 1996). This repair process may be one of the causal factors in smooth muscle hypertrophy (Persson et al., 1996). Rennard proposed that this abnormal repair process is an important potential therapeutic target.

Non-eosinophilic asthma

Some patients with asthma do not present with the typical indicators of a high level of eosinophil numbers and activity. In a small uncontrolled study, symptomatic

patients with eosinophil counts in the normal range had a poor response to inhaled corticosteroids (Pavord, Brightling, Woltmann, & Wardlaw, 1999). High dose corticosteroid dependent patients with severe asthma were found to have eosinophil levels in bronchoalveolar-lavage (BAL) fluid that were not significantly different from normal controls, while those with moderate asthma had high levels (Wenzel et al., 1997). However, corticosteroid dependent patients had significantly higher concentrations of neutrophils in BAL fluid. Leung & Szefler (1999) propose that this is a newly identified form of airway inflammation.

Assessment and Diagnosis

Objective measures of lung function can be obtained with computerized spirometry in the outpatient clinic or research laboratory. At home patients can objectively measure one aspect of lung function, the peak expiratory flow (PEF), using a handheld meter. The most common objective assessment of lung function is the forced vital capacity maneuver performed with a computerized spirometer. A brief overview of the structure of the lungs and how lung function is assessed will assist those not familiar with the physiology of asthma to interpret this study.

Normal lung structure

The trachea divides into the left and right main bronchi with progressive division to an average of 23 generations (Grippi, 1995). The first 16 generations (conducting airways) transport air to the gas-exchanging regions of the lung. The alveoli are the final generation of airway in the gas-exchanging region. There are approximately 300 million alveoli in our lungs. The conducting airways are lined with shorter and taller epithelial cells, creating a layer-like structure, the pseudostratified epithelium. Goblet cells secrete a blanket of mucus that coats the airways. The mucus blanket is moved toward the airway opening by cilia on the surface of the epithelial cells. The epithelial cells are attached to the basement membrane, outside of which is the submucosal connective tissue containing bundles of airway smooth muscle (ASM). ASM is present in the conducting and gas-exchanging regions, extending as far in the periphery as the openings of the alveoli. Although the airways become progressively smaller as they divide, the total

cross-sectional area of the airways becomes larger because of the increase in number of airways. This increase in cross-sectional area has an important effect on the resistance to airflow in the large vs. small airways. Resistance to airflow is partly dependent on the lung volume. At higher lung volumes, the walls of bronchi are pulled to a larger diameter by the elastic tension of the alveolar walls (tethering effect) (Leff & Schumacker, 1993). At low lung volumes, decreased tethering effect results in narrower airways and increased resistance. Some airways become so narrow that they close at low lung volumes (closing volume). Parasympathetic nervous system tone changes as stretch receptors in the ASM detect changes in lung volume (Leff & Schumacker, 1993). As volume increases, parasympathetic tone is decreased, reducing constriction of ASM. As volume decreases, parasympathetic tone is increased, constricting ASM and increasing resistance to airflow.

Due to the reserve capacity of the respiratory system, lung disease may not affect normal breathing until advanced stages (Leff & Schumacker, 1993). To assess lung function, patients may be asked to perform maneuvers that stress the capacity of the respiratory system. The most commonly used forced exhalation test is the forced expiratory vital capacity (FVC) maneuver (Hyatt, Scanlon, & Nakamura, 1997). During forced expiration, the rate of airflow and change in volume of air are plotted as a flow-volume curve. Plotting both the inspiration and expiration creates a flow-volume loop (FVL). Values obtained during the FVL are compared to predicted values determined by norming studies.

The FVC maneuver is valuable in that it measures the maximum flow at different lung volumes (Hyatt et al., 1997). The maximum flow is affected by even mild manifestations of various lung diseases. The highest flow rate, achieved at the start of the maneuver (greatest lung volume), is the peak expiratory flow (PEF). PEF is an indicator of the calibre of the bronchi and larger bronchioles (large airways). PEF is partly influenced by the strength of the respiratory muscles and can be increased with physical training (Cotes, 1993). After approximately 30% of the VC has been expired, the maximal flow rate is dependent on lung volume and is relatively independent of effort (Cotes). Increased effort does not increase the flow rate.

Two important clinical measures provided in a FVC maneuver are the forced expiratory volume in one second (FEV_1) and mean forced expiratory flow between 25% and 75% of the expired vital capacity ($FEF_{25-75\%}$). PEF, FEV_1, and $FEF_{25-75\%}$ are measured in litres of air per second (L/s).

Spirometry Interpretation

Performance on the forced exhalation test assists in determining presence and severity of various lung diseases. There are two main categories of abnormal physiological lung function: obstructive and restrictive (Kelly, 1995). Increased airway resistance characterizes obstructive disorders, such as asthma. Between asthma attacks, lung volume (VC) may be normal compared to predicted values. Increased airways resistance may be indicated by lower than predicted measures of airflow (e.g., FEV_1).

In restrictive disorders (e.g., pulmonary fibrosis), the characteristic limited inflation of the thorax may be indicated by lower than predicted VC and a decrease in the force of expiratory airflow (lower FEV_1). Please note that clinical presentation may be more complicated than suggested by these examples. The plot or tracing obtained during the FVL can be visually examined for patterns that are characteristic of different lung diseases.

In asthma, one of the factors causing increased airway narrowing and airway resistance is contraction of ASM (also known as bronchospasm or bronchoconstriction). Once an initial FVL is obtained, the degree of bronchoconstriction can be assessed by administering a fast acting bronchodilator then obtaining another FVL. Improvement in parameters of lung function following a bronchodilator suggests bronchospasm is at least partly involved in the airway obstruction (Kelley, 1995). A diagnostic feature of asthma is a 12% improvement in FEV_1, with a volume change of at least 180 mL, following administration of beta$_2$-agonist (Boulet et al., 1999). This change in FEV_1, commonly referred to as "reversibility", indicates variable airflow obstruction (a cardinal feature of asthma).

Post-bronchodilator FEV_1 provides a measure of lung function in which daily factors of bronchospasm, such as exposure to environmental stimuli are minimized (Enright et al., 1994). Post-bronchodilator changes in FEV_1 may be minimal or non-

existent in those with mild or severe airways obstruction. With mild obstruction, airways may be near or at maximal dilation. In the case of severe obstruction, with edema and secretions blocking the airways, the airways do not respond rapidly to the bronchodilator (Enright et al.).

$FEF_{25-75\%}$ reflects small airways calibre (Cotes, 1993). A lower that predicted FEF_{25-75} will indicate small airways obstruction in asthma. This measure is considered by some to be useful in detecting early stage airways obstruction (Cotes, 1993; Hyatt et al., 1997). Some patients with primarily small airways obstruction may display significantly lower than predicted $FEF_{25-75\%}$ yet have FEV_1 in the normal range (greater than 80% of predicted value). Clinical interpretation of $FEF_{25-75\%}$ must consider changes in FEV_1 and FVC. An increase in FEV_1, which is clinically desirable, may result in a decrease in $FEF_{25-75\%}$ as the patient was able to expire a larger volume of air in the early part of the FVC maneuver due to decreased airways resistance.

Home monitoring of PEF

Peak expired flow (PEF) can be measured by patient at with a Mini-Wright Peak Flow Meter (MPFM). The MPFM is a portable, lightweight instrument designed for self-monitoring of lung function. Its use is frequently recommended by physicians and asthma education programs to enable individuals with asthma to objectively monitor changes in lung function that occur well before changes in subjective symptoms are recognized.

While PEF measured with a MPFM is obtained in ambient conditions, PEF obtained with a spirometer is expressed in body temperature and pressure saturated with water vapour conditions (BTPS). Long-acting bronchodilators are withheld prior to spirometry but not prior to home monitoring of PEF. Because airways are typically well dilated in patients taking long-acting bronchodilators, changes in airway inflammation may be masked by consistently high PEF readings and minimal symptoms.

PEF measurements have twice the variability of FEV_1 (Enright et al., 1994). PEF is a reasonable predictor of FEV_1 and $FEF_{25-75\%}$ although increased airtrapping in moderate to severe asthma can contribute to misleadingly high PEF readings (Eid, Yandell, Howell, Eddy, & Sheik, 2000). Compared to FEV_1, PEF measurements can underestimate airway obstruction (Klein, Fritz, Yeung, McQuaid, & Mansell, 1995).

Diagnosis

In addition to symptoms and clinical history, asthma has three features that can be used to establish a diagnosis: variable airflow obstruction, bronchial hyperresponsiveness (BHR), and airway inflammation. Spirometry showing an improvement of at least 12% in FEV_1, with a volume change of at least 180 mL, following administration of $ß_2$-agonist is the preferred method of diagnosis (Boulet et al., 1999). Spirometry can be used with adults and most children. When reliable spirometric measures are unattainable with a child, factors considered in making the diagnosis include: history of wheezing, family and personal history of asthma and atopy, and clinical benefit from bronchodilators or anti-inflammatory therapies (Boulet et al.). Asthma can also be diagnosed with a 20% improvement in FEV_1 following therapy with corticosteroids or airway hyperresponsiveness indicated by a provocation test with histamine or methacholine (Boulet et al.).

The severity of asthma can be defined according the treatment required to maintain acceptable control or FEV_1 percent of predicted (Boulet et al., 1999). For example, a patient may be considered to have "mild" asthma if well-controlled symptoms are maintained with occasional use of short-acting $ß_2$-agonist and low-dose inhaled glucocorticosteroid. Asthma is considered "severe" if short-acting $ß_2$-agonist, high doses of inhaled glucocorticosteroid, and additional therapies are required to maintain well-controlled symptoms. Asthma is also considered severe or poorly controlled if the patient had a near-fatal episode, recent emergency visit or hospital admission, night-time symptoms, limitation of daily activities, use of inhaled $ß_2$-agonist at night or several times a day, and/or FEV_1 below 60% of predicted values (Boulet et al.). Based on spirometry patients can be classified as mild, moderate, or severe, if their FEV_1 is >80%, 60-80%, or <60% of predicted, respectively.

Treatment

Pharmacotherapy for asthma includes "reliever" medications, which cause rapid bronchodilation to relieve acute symptoms, and "controller" medications, which treat the airway inflammation and provide long acting bronchodilator effects. Inflammation is the

underlying mechanism for the development of asthma symptoms and airflow limitation, and therefore is the main target of asthma therapies.

Asthma Control

The Canadian Asthma Consensus Report (Boulet et al., 1999) and the recent update to these guidelines (Boulet et al., 2001) recommended that asthma treatment be based on the goal of achieving a level of acceptable asthma control. Asthma control may be achieved with combinations of pharmacotherapy, avoidance of environmental allergens and irritants, and patient education. Even with adequate treatment, many individuals with asthma will continue to have symptoms, require the use of a rescue bronchodilator, and demonstrate impaired pulmonary function.

Bronchodilators

Bronchodilators relieve airway smooth muscle constriction, controlling symptoms and maintaining airway calibre, but do not reduce airway inflammation. Short-acting β_2-agonists are used to quickly relieve acute asthma symptoms and prevent symptoms from occurring when used prior to exercise or sexual activity. Their maximum effect occurs within 10-15 minutes and lasts for 2-6 hours.

Boulet et al. (1999) recommended that short-acting β_2-agonists may be used alone to treat very mild asthma. However, if the short-acting β_2-agonist is used as rescue medication more than 3 times a week, an inhaled glucocorticosteroid should be added to the treatment (Boulet et al.). Responding to severe asthma exacerbation solely by increasing the frequency of short-acting β_2-agonist usage may result in temporary relief from symptoms while the inflammatory process continues unabated. Regular use of short-acting β_2-agonists may also lead to tolerance of the bronchoprotective effect (Cockcroft & Swystun, 1996). Airway obstruction may progress to a degree that the short-acting β_2-agonists are unable to maintain adequate airway calibre. These patients frequently require intensive therapy in the emergency department to relieve their acute and life threatening symptoms. If regular bronchodilator treatment is required for control of asthma symptoms, long-acting bronchodilators are preferred over short-acting β_2-agonists (Sears, 2000).

The molecular target for β_2-agonists is the β_2-adrenergic receptor. Genetic variations in β_2-adrenergic receptors may influence asthma severity and response to β_2-agonist treatment (Liggett, 2000). Response to short-acting β_2-agonists may be impaired during viral respiratory infection related exacerbation. In a study of 43 patients with poorly controlled asthma, average post-bronchodilator PEF was 28% higher than average pre-bronchodilator PEF, while there was only mean increase in PEF of 1% following bronchodilator during viral respiratory infection (Reddel et al., 1999).

Long-acting bronchodilators are taken regularly to maintain airway calibre and not for treatment of acute bronchospasm. The onset of action is slow, but the bronchodilatory effect is prolonged. Long-acting bronchodilators include: inhaled β_2-agonists (Salmeterol and Formoterol), theophylline, and Ipratropium. In moderate asthma, adding Salmeterol may be more effective in controlling symptoms than increasing the dose of corticosteroid (Woolcock, Lundback, Ringdal, & Jaques, 1996).

Ipratropium bromide is an inhaled anticholinergic agent that has a slower onset of action than short-acting β_2-agonists. It can be a useful addition to a short-acting β_2-agonist, providing greater bronchodilation than a β_2-agonist alone (Qureshi, Pestian, Davis, & Zaritsky, 1998). As well, Ipratropium may be used for patients who are intolerant of short-acting β_2-agonists (Boulet et al., 1999).

Side effects. Patients without sufficient education about the nature of asthma and the medications they use may overuse short-acting β_2-agonist bronchodilators. Frequent use of these medications masks symptoms of increasing airway obstruction. Patients may delay seeking medical attention until airway inflammation is severe and β_2-agonists fail to reduce bronchoconstriction.

Taylor et al. (1996) found that delays in treatment resulting from frequent use of highly effective bronchodilators do not explain the increasing prevalence of severe asthma and increased hospital admission rates. They hypothesized that increased bronchial hyperresponsiveness to allergen and decreased baseline lung function caused by long-term use of short-acting β_2-agonists may create a cycle of increasing asthma severity and escalating short-acting β_2-agonist usage. This deterioration of asthma associated with long-term short-acting beta-agonist use may occur despite adequate anti-

inflammatory therapy. Prolonged use of inhaled bronchodilators has been associated with increased bronchial hyperresponsiveness to allergen, decreased baseline lung function, and increased mortality (Taylor et al., 1996; Beasley et al., 1999).

Corticosteroid Anti-inflammatories

Topical. With the exception of the mildest cases, inhaled glucocorticosteroids are preferred as the first line of anti-inflammatory treatment for asthma (Boulet et al., 1999). The finding of persistent inflammation with mucosal eosinophilic infiltration in allergic rhinitis, even in the absence of symptoms, provides additional support for treating the inflammatory component of even mild airway inflammation (Ricca et al., 2000).

Boulet et al. (1999) recommends treating asthma with an initial dose of inhaled glucocorticosteroid in the range of 400-1000 μg. Doses higher than 1000 μg may be required for severe asthma. With doses greater than 1.5 mg per day, marked adrenal suppression occurs (Lipworth, 1999). Inhaled corticosteroids have a relatively flat dose-response curve so increasing the dosage may not always improve lung function (Barnes, 1998). In these cases, the addition of long acting bronchodilators or nonsteroidal anti-inflammatory may be a preferable alternative.

Although safer than oral corticosteroids, inhaled corticosteroids are not without their risks. In a recent study of patients aged 20-40 years taking inhaled corticosteroids for a minimum of 6 months (median of 6 years, range 0.5 to 24 years), inhaled corticosteroid use was associated with a decrease in bone-mineral density at the spine and proximal femur equally in men and women (Wong et al., 2000). Use of inhaled corticosteroids has been associated with glaucoma (Cummings, Mitchell, & Leeder, 1997) and cataracts (Pauwels et al., 1999). Significantly reduced growth rates in children have been documented with 400μg/day of beclomethasone dipropionate (Simons, 1997). Because of individual variability in developing systemic side effects, Apgar (1999) recommended regular examinations for patients on long-term inhaled corticosteroid therapy.

Systemic. While treatment with inhaled corticosteroids is preferable, oral corticosteroids may be used in bursts for control of exacerbations or long-term in cases of severe asthma that do not respond well to inhaled anti-inflammatories. Boulet et al.

(1999) recommended that oral prednisone should be considered if the patient's expiratory flows are less than 60% of predicted value and symptoms are frequent. Side effects are more frequent and severe with oral than inhaled corticosteroids. Bone mineral density declines two times faster, and risk of hip fracture is 2·1 for women taking oral corticosteroids compared to non-users (Baltzan et al., 1999).

Corticosteroid-Resistant asthma

Although most patients respond to corticosteroids with improved lung function, a small proportion fail to respond or have minimal response. Prevalence of complete corticosteroid resistance is less than 1 in 1000 asthmatic patients (Barnes, 1998).

Non-steroidal anti-inflammatories

Cromolyn sodium (Intal) and nedocromil sodium (Tilade) are non-steroidal anti-inflammatories. Cromolyn inhibits mast cell degranulation, has no bronchodilating activity, but can decrease airway hyperresponsiveness. Both cromolyn and nedocromil have been shown to have anti-inflammatory properties since they can down regulate eosinophil and neutrophil agonist induced activation (Moqbel, 1999).

Alternative

Other classes of medications that often complement inhaled corticosteroids are theophylline and the antileukotrienes. Theophylline may have a modest anti-inflammatory effect (Weinberger & Hendeles, 1996) and can decrease the severity and frequency of symptoms in persistent asthma (Evans, Taylor, Zetterstrom, Chung, & O'Conner, 1997). However, clinical significance of the immunomodulatory effects of theophylline has not been demonstrated (Boulet et al., 1999). Of the antileukotrienes, zileuton (Zuflo) inhibits leukotriene synthesis and zafirlukast (Accolate) as well as montelukast (Singulair) are leukotriene-receptor agonists. Boulet et al. recommended that leukotriene-receptor agonists be considered as an adjunct to corticosteroids to control persistant symptoms and avoid increasing corticosteroid dosage. Leukotriene-receptor agonists are not recommended for the treatment of mild asthma (Boulet et al.).

Education and Environmental Control

Environment is the principal determinant of asthma prevalence (Burney, 1993). Proper control of the environment to reduce exposure to irritants and allergens is crucial.

Treatment with asthma medications should not be a substitute for adequate environmental control (Boulet et al, 1999). Boulet et al. state that an essential component of asthma therapy is education with the goal of "control of asthma via improved knowledge and change in behaviour" (p. 15).

Indoor allergens are a significant factor in asthma development and exacerbation. Common indoor allergens include cockroach, dust-mite, and cat. Among American inner city children, sensitization to cockroach allergen was associated with significantly higher rates of asthma related unscheduled medical visits and hospital admissions than allergies to other allergens (Rosenstreich et al., 1997). Dust-mite allergy, but not cat or cockroach sensitization, was independently associated with asthma in Virginia high school students (Squillace et al., 1997).

Public places such as schools, that do not have resident animals, may still be contaminated with animal allergens. A longitudinal study of schools in Sweden (grades 1 and 2) found a significant association between asthma and sensitization to animal dander and birch allergens (Perzanowski, Ronmark, Nold, Lundback, & Platts-Mills, 1999). Samples from the desks and chairs in the schools found moderate levels of dog and cat allergen in 97% of samples. School was possibly the most important site of exposure to cat allergen as IgE antibodies did not correlate with presence of a pet in the home.

Hygiene hypothesis. While minimizing indoor allergens is important for those with atopic asthma, an environment that is too "clean" may contribute to the development of asthma. The "hygiene hypothesis" proposes that lack of exposure to immune system challenges in early life may be related to high prevalence of allergies and asthma in industrialized countries. Chronic exposure to indoor bacterial endotoxins may enhance type 1 T-helper cell immunity (releasing Interferon-γ) and protect against allergen sensitization (Gereda et al., 2000). Absence of microbial burden on the immune system in infancy may delay maturation of immune responses (switch from type 2 to type 1 T-helper cells), resulting in a predominately type 2 T-helper cell immune response (generating IL-4, IL-13 and IL-5) to environmental antigens (Martinez, 1999; Martinez & Holt, 1999). Martinez & Holt proposed that chronic airway inflammation during the

physical development of lungs in childhood may be related to the development of bronchial hyperresponsiveness.

Psychoneuroimmunology

Psychoneuroimmunology (PNI) is the study of behavioural-neural-endocrine-immune system interactions (Ader, Cohen, & Felten, 1995). The many bi-directional molecular and biochemical interactions between the nervous system and immune system have been documented in hundreds of animal and human studies. A detailed presentation of the nervous-immune pathways is beyond the scope of this review. Numerous reviews detailing this interaction are available (e.g., Cohen, Ader, & Felton, 1994; Bateman, Singh, Kral, & Solomon, 1989).

As early as the 1920's, conditioned immunosuppression and conditioned enhancement of immunologic reactivity has been documented in animal studies. The immune system can be conditioned to respond through classical conditioning or one trial association learning. The ability to condition immune responses to sensory input is strong evidence of a neuro-immune connection.

In an animal study, Ader and Cohen (1975) conditioned the immunosuppressive effect of cyclophosphamide to saccharine-flavored water using only one conditioning trial. They later used this cyclophosphamide-saccharine conditioned response in the experimental treatment of disease prone mice (Ader & Cohen, 1982). Using consecutive pairings, Spector (1987) conditioned increased natural killer (NK) cell activity to the smell of camphor. Immunosuppression can also be conditioned to stressors such as electric foot shock (Lysle, Cunnick, Fowler, & Rabin, 1988).

The approach to conditioning an immune response used by Ader and Cohen (1975) was successfully applied in the treatment of a patient with severe lupus (Olness, 1993). The immunosuppressive effect of cyclophosphamide was conditioned to the scent of perfume and the taste of cod liver oil in 3 pairings. In treatment, the administration of cyclophosphamide was alternated with the perfume/oil stimulus, permitting a reduction in the total amount of drug given while maintaining the desired level of immunosuppression.

It is clear that immune responses are easily conditioned. Unintentional conditioning may be a component in a patient's response to treatment. For example, women who had previously received immunosuppressive chemotherapy were documented to have immunosuppression as a result of returning to the physical environment of the hospital (Bovjberg et al., 1990).

Stress and Immune Suppression

For the psychologist, it is important to understand that stress and negative mood states can alter normal immune function and contribute to the onset or exacerbation of disease. Alternatively, psychological treatments that decrease stress or depression may be of benefit to patients with physical disease.

While the body may respond to a very brief negative mood state with enhanced immune function (Futterman, Kemeny, Shapiro, & Fahey, 1994), significant stressors may cause suppression of various immune parameters. Immunosuppressive effects of stress have been extensively studied. Only a few studies will be mentioned here.

Academic stress has been associated with decreased memory T-cell proliferation (Glaser et al., 1993), decreases in production of γ-interferon by concanavalin A-stimulated lymphocytes, T-cell killing by memory T lymphocytes of EBV transformed autologous B lymphocytes (Glaser et al., 1987), and decreased NK cell activity (Kiecolt-Glaser, et al., 1984). Sleep deprivation has been shown to suppress NK cell activity (Irwin et al., 1994).

Stress before and during a 15-week study was found to be associated with increased risk of upper respiratory tract illness (Turner, Cobb, & Steptoe, 1996). The effect of stress on illness was reduced by social support and an avoidant psychological coping style.

The 90 to 120 minute cyclings of our body's ultradian rhythms can be disrupted by psychological and physiological factors such as stress. Disruption of these rhythms has been attributed as a cause of psychosomatic illness (Rossi 1996).

Depression

Depression has been linked to suppressed immune function and increased risk of disease. Levy, Herberman, Lippman, and d'Angelo (1987) found that radiation or chemotherapy did not significantly change NK cell activity in women with breast cancer. However, reports of depressive, fatigue-like symptoms, and lack of social support in the same patients were associated with decreased NK cell activity.

The Western Electric Health Study (WEHS) was a prospective longitudinal study to investigate coronary heart disease. Several studies examined the WEHS data to examine the relationship between cancer and psychosocial characteristics. Depression, indicated by elevated scores on the Minnesota Multiphasic Personality Inventory (MMPI) was significantly associated with increased risk of death from cancer but not increased risk of any other cause of death (Persky, Kempthorne-Rawson, & Shekelle, 1987; Shekelle et al, 1981). The relationship between depression and cancer was independent of age, body mass index, cigarette smoking, alcohol consumption, family history of cancer, serum cholesterol, and occupational status.

Personality

There is some evidence that certain personality characteristics may be associated with the development of physical disease. A tendency to be emotional and outwardly express those emotions is associated with the lowest risk of cancer, while those categorized as loners have the highest risk (Shaffer, Graves, Swank, & Pearson, 1987). Similarly, Grossarth-Maticek, Siegrist, and Vetter (1982) found that repressive communication style (submissive, non-aggressive, and self-derogative) was related to incidence of cancer in European males and females.

Obesity

Severe obesity is associated with disturbances of the hypothalamo-pituitary-adrenal (HPA) axis and immunological dysfunctions, including: hypercortisolism, leukocyte dysfunction, and cytokine abnormalities (Kral, 2001). Prevalence of asthma in severely obese patients is 10-20% (Kral, 2001). Obesity is a risk factor for asthma and is associated with poor asthma control. Atopy was found to be more common among individuals with a large body mass index (Xu, Jarvelin, & Pekkanen, 2000).

Public Awareness of PNI

Cousins (1979) and Siegel (1986) raised public awareness of the connection between mind and body. Their best selling books presented reviews of PNI research and many anecdotal reports of disease remission attributed to psychological factors. Cousins extrapolated from research that linked negative emotions with negative effects on health and developed a program to produce positive emotions as a self-treatment for a serious collagen disease that left him bed ridden and in constant pain. On a daily basis he watched comedy classics such as episodes of "Candid Camera" and listened to humor books read to him by nurses.

Siegel attributed spontaneous cancer remission to positive mood states and certain patient characteristics (e.g., interest in education about their disease, assuming some of the responsibility for their medical treatment, and an inner locus of control). The increased public awareness of the psychosocial factors of disease was important in stimulating research in PNI and the development of clinical approaches such as mental imagery techniques for regulating the immune system. This popularization of mental imagery treatment has not been without criticism. Cassileth (1990) asserted that there is no evidence supporting the position that mental imagery can influence the immune system and that imagery has "attained the status of a national cult" (p. 81). He speculated that psychologically influenced immune changes will likely be too transient and minor to have a significant impact on disease. As well, he raised the concern that guilt may occur in those who fail to attain self-cure.

Intentional Immunomodulation Research

There is a long history of anecdotal reports (e.g., Erickson, 1977a) and research on the ability of individuals to voluntarily alter autonomic physiological processes during hypnosis (see Barber, 1978 and Barber, 1984 for extensive reviews). As early PNI research documented the neural and chemical connections between the mind and immune system, psychologists began to rigorously examine if hypnotic techniques could alter immune function. I will review several landmark studies and where applicable, present the treatments in more detail. Most relevant to asthma, are the studies that documented

changes in neutrophil adhesion following practice of relaxation assisted mental imagery (e.g., Hall et al., 1996).

Immunoglobulins. Olness, Culbert, and Uden (1989) examined the effects of hypnosis on salivary immunoglobulins (sIgA) in children between the ages of 6 and 12. The children were randomly assigned to 3 groups. After providing baseline samples of saliva, all participants received education about the immune system via videotape. Two weeks later the children returned and provided a second baseline sample. Treatments were administered and a third (post-treatment) sample was collected. Treatment for Group A consisted of listening to a 25 minute self-hypnosis tape and "non-specific" suggestions that immune substances in the saliva might increase. Group B received a similar treatment except the suggestions specified increased salivary immunoglobulins. Group C, a control group, conversed for 25 minutes. Group B demonstrated a statistically significant increase in sIgA between samples 2 and 3, $p = .007$. There were no significant differences between the groups on the Stanford Children's Hypnotic Susceptibility Scales, nor was there any association between hypnotic susceptibility scores and sIgA change within group B.

Rider and Weldin (1990) examined the effects of music and imagery on immune function. Students ($N = 30$) were randomly assigned to 3 groups: imagery/music, music, and control. A brief explanation on antibodies was provided to the imagery/music group. Saliva was collected before and after a ten minute treatment period for all groups. Treatment for the imagery/music group consisted of imagining antibody production listening to music specifically composed to facilitate relaxation. The music group listened to the music and was attentive to any feelings or imagery that might spontaneously develop. The control group sat in silence for the 10 minute treatment period. The imagery/music group had an increase in sIgA levels which was significantly greater than in the music or control groups, $p < .0001$. Mean changes in sIgA for the imagery/music, music, and control groups were, respectively, 30.72, 6.45, and -1.23.

Natural Killer cells. Natural killer cell function is important in a number of diseases including cancer. In 10 healthy subjects, natural killer cell function significantly

increased following relaxation and imagery of immune change compared to a control condition of relaxation imagery alone, $p < .05$ (Zacharie et al., 1990).

Hypersensitivity reactions. Several studies provide evidence of intentional modulation of immune response to antigen challenge. In an A-B-A design single case study, a delayed hypersensitivity reaction to Varicella zoster was inhibited with mental imagery practice during daily meditation (Smith et al., 1985). Baseline, treatment, and withdrawal phases of the experiment were each 3 weeks long. Measurements of size of induration and lymphocyte stimulation were significantly different between the experimental phase and the control phases ($p < .001$). Nine months later, the experiment was reproduced with the same subject, again with statistically significant differences between experimental and control phases.

Smith et al. (1985) provided a detailed description of the method used by the subject who successfully inhibited the delayed hypersensitivity reaction:

> She would usually reserve about five minutes of her daily meditation for attention to the study. First she would dedicate her attention concerning the study for universal good instead of self-advancement. She would also tell her body not to violate its wisdom concerning her defense against infection. Finally she would visualize the area of erythema and induration getting smaller and smaller. Soon after each phase 2 injection, she would pass her hand over her arm, sending "healing energy" to the injection site. (p. 2111)

Subsequent studies examining attempts at voluntary modulation of delayed hypersensitivity reactions have been less successful. Following hypnosis and imagery representing an altered immune response, significant changes in skin response to Varicella zoster was documented. However, there was no significant change in lymphocyte stimulation (Smith et al., 1992). No significant modulation of delayed hypersensitivity reactions to skin challenges with various antigens was documented following hypnotic suggestions to enhance or suppress immune reaction (Locke et al., 1987).

Two important studies provide evidence that levels of salivary immunoglobulins may be increased with psychological techniques. Compared to controls, sIgA in children between the ages 6 and 12 significantly increased following education about the immune system and hypnotic suggestions of increased salivary immunoglobulins, $p = .007$ (Olness, Culbert, & Uden, 1989). Rider and Weldin (1990) compared the effects of relaxing music and imagery representing antibody production with two control conditions (relaxing music or sitting in silence). After only a 10 minute treatment period, sIgA levels were greater in the imagery/music group than in the music or control groups, $p < .0001$.

Neutrophils. Neutrophil adhesion to vascular endothelial cells is necessary for the neutrophil to migrate across the endothelium (wall of the blood vessel) and accumulate at extravascular sites of infection and/or inflammation (Godin, Caprani, Dufaux, & Flaud, 1993). Neutrophils constitute over 70% of all leucocytes (Male 1991) and although they protect the body they are also involved in disease pathology. Neutrophils must become active and produce proteins on the surface of the cell to first adhere to, and then migrate across the endothelium. After penetrating the wall of the blood vessel the neutrophils accumulate at sights of infection or inflammation. In asthma, adhesion is also a crucial component in the movement of eosinophils to the airway lumen.

Intentional alteration of leukocyte adhesion demonstrated in several studies has important implications in inflammatory conditions such as asthma. Rider and Achterberg (1989) examined the effect of cell specific imagery to influence either neutrophils or lymphocytes. Thirty subjects were randomly assigned to two experimental groups each of which practiced an imagery treatment to enhance immune function. One group focused on lymphocytes while the other group focused on neutrophils. The two initial sessions included education about the morphology and location of lymphocytes or neutrophils and imagery development. After six weeks of home practice with the aid of an audio taped Jacobson progressive muscle relaxation protocol, peripheral blood samples were taken before and after a final 20 minute imagery session. Lymphocytes, but not neutrophils, decreased significantly in the group imagining changes in lymphocytes. Similarly, in the neutrophil group, there were significant decreases in neutrophils but not

lymphocytes. Rider and Achterberg hypothesized that the cell counts decreased as a result of increased cell migration out of the blood stream. This early study provided an indication that imagery could be used to selectively target specific immune cells and that immune changes can occur rapidly (within 20 minutes).

The efficacy of mental imagery in altering neutrophil adhesion was examined in several controlled studies. Hall, Minnes, Tosi, and Olness (1992), assigned normal subjects (N =45) to 3 groups. All subjects attended two treatment sessions a week apart. During each session peripheral blood samples were taken before and after a 30 minute intervention. Subjects in the control condition (group A) were instructed to rest during the 30 minute period. There was no change in adherence in session 1, demonstrating stability of the measure. Control subjects were instructed to practice resting daily for 1 week then return for session 2. Again, no significant change in neutrophil adhesion occurred during the 30 minute rest period. Group B was provided education about neutrophils and instructed to create imagery to represent increased adherence then practice the imagery following a relaxation induction. In session 1 there was a significant pre-to-post decline in neutrophil adherence during the 30 minute intervention, $t = -2.859$, $p = .01$. In session 2, after one week of daily practice relaxing and imaging, there was a clear but not statistically significant decrease in adherence. Thus, while imagery represented increased adherence, neutrophil adhesion actually decreased. Group C received training in self-regulation prior to beginning the treatment phase identical to group B. The training consisted of 4 sessions of training in relaxation and imagery that focused on decreasing sIgA. There was a decrease in adherence in session 1 and an increase in adherence in session 2. There were no significant changes in chemiluminescence, neutrophil count, monocyte count, platelet count, white blood count, or salivary IgA. Changes in neutrophil adherence were not associated with high hypnotic ability. There was no relationship between pulse rate or temperature (indicators of relaxation) and changes in neutrophil adherence (Hall et al., 1993). In session 1 and 2 for group B and session 1 for group C the effect on adhesion was opposite to that which was intended (increased adhesion). Only in session 2 for group B did adhesion increase as intended. Hall et al. (1992) noted that a learning curve has been observed in self-

regulation training and speculated that this learning curve may be responsible for the inconsistent results. Dr. Hall (personal communication, May 15, 1995) stated that the increase in adherence seen in session 2 for group C of the 1992 study may have been the result of the relaxation component taking effect.

A follow-up study was conducted to further examine the effects of imagery on neutrophil adhesion (Hall, Papas, Tosi, & Olness, 1995). Although the small sample size (N = 15) limited the findings, some statistically significant changes in neutrophil adhesion did occur. Members of the control group (group 1, n = 8) rested with eyes closed, while two experimental groups practiced imagery representing decreased adherence (group 2, n = 4) or increased adherence (group 3, n = 3). All groups received basic education about the immune system and had 4 sessions of practice and training prior to session 1. Pre- and post imagery blood samples were collected in session 1 and session 2, two weeks later. Group 1 had an increase in adherence, and Groups 2 and 3 had clear decreases in adherence. Only the decrease for the group 3 was statistically significant. Hall et al. speculated on possible reasons for the observed effects. First, they note that stress can decrease neutrophil adherence and suggest that the task of practicing immune imagery may have placed strong demands on subjects evoking some degree of stress. Second, they speculate that the process of the intervention may be related adhesion changes. For example, decreased adhesion may be related to "active-imaging" while increased adherence may be related to "passive-resting". However, if passive resting increases adherence, why did adherence remain unchanged in the resting control condition of Hall et al. (1992)?

Mast cells. Olness, Hall, Rozniecki, Schmidt, and Theoharides (1999) conducted an interesting study on migraines that may have implications for asthma treatment. The release of histamine and other molecules by mast cells in the dura, possibly in response to stress, has been linked to the onset of migraine headaches. Out of 14 children who experienced regular episodes of migraine (between 4 and 5 per month) and practiced relaxation imagery, 10 had a reduction of frequency to one episode per month or less. Eight of these 10 children had a significant decrease in urine tryptase compared to baseline. Olness et al. speculate that conditioned relaxation may be an inhibitor of mast

cell activation. Modulation of mast cell activity is desirable in asthma. I wonder if the hypothesized relaxation-mast cell interaction occurs with mast cells resident in the airways of asthma patients. If so, this interaction may explain some of the reported benefits of relaxation therapies as adjunct treatments for asthma.

Warts. Although studies on wart regression following psychological interventions have not typically included any measures of immune function, they still provide an example of treatment efficacy in a clinical population. Numerous case studies of the hypnotic treatment of warts are available (e.g., Rowe, 1982; Tasini & Hackett, 1977). Barber (1984) provides a thorough review of the clinical and experimental use of hypnosis in the treatment of warts.

The results of one study suggests that hypnosis may be more effective as a treatment for warts than currently prescribed topical treatment. Subjects who received treatment with hypnotic suggestions and imagery of wart regression had significantly more wart regression than those who received a common topical treatment (salicylic acid), a placebo topical treatment, or no treatment (Spanos, Williams, & Gwynn, 1990).

However, not all studies in this area were conclusive. Relaxation mental imagery was not associated with wart regression in a recent multi-centre controlled study (Felt et al., 1998). The treatment consisted of relaxation and instructions to "imagine not feeding their wart(s) anymore 'so the wart(s) will go away' and how pleasant their extremity would appear without the wart(s)" (Felt et al., p. 132). Although wart regression was documented in the mental imagery group, the change was not statistically significant compared to standard topical treatment or no treatment conditions. Follow-up 6 and 12 months after the study revealed that 79% of the children in the mental imagery group reported they had used the relaxation and mental imagery techniques to help with sports, school pursuits, or pain control. Although the study had 61 participants, power was low with only a 20 to 25% probability of rejecting the null hypothesis. At a 95% confidence level, 160 participants would have been required for adequate power. In retrospect, Felt et al. questioned the appropriateness of the instructions for the wart regression imagery and note that other studies have used suggestions of warm or a tingling sensation.

Wound Healing. Probably the most dramatic example of the mind's ability to influence the immune and healing functions of the body is provided with the Deliberately Caused Bodily Damage Phenomena (DCBD) observed in various cultures (Hussein, Fatoohi, Hall, & Al-Dargazelli, 1997). Individuals will pierce their bodies with sharp objects, penetrating skin, muscle, and even viscera. Unusually fast healing and complete control of infection, bleeding, and pain has been documented (Hussein et al.).

Pathways of Mind-Body Communication and Healing

How DCBD or intentional immunomodulation occurs is still poorly understood. However, research has identified various pathways of communication within the mind and body that may be involved. Psychoneuroimmunology research has revealed an integrated biological network formed by complex interrelationships among behavioral, neural, immune and endocrine processes (Song & Leonard, 2000). Neural and chemical communication between these systems is involved in both the harmful physiological effects of stress and potentially beneficial intentional alteration of immune function using psychological techniques. Rather than reviewing the often-cited typical responses to stress via the autonomic nervous system and endocrine system as evidence of the mind-body connection, I will summarize part of Rossi's (1993, 1994, 1998) theory of mind-body communication and healing. Integrating research in the areas of neuroimmunology, endocrinology, genetics, chronobiology, hypnosis, and voluntary immunomodulation research, Rossi's reviews are helpful to the psychologist interested in the mind-body connection and implications for treatment of physical disease.

Rossi (1998) describes the "complex field of mindbody communication and healing" in terms of four major components: limbic-hypothalamic-pituitary system; immediate early genes in psychobiological adaptation; new protein synthesis in stress, trauma and healing; and messenger molecules and state dependent memory (p. 1). In the first stage, mental experiences are transduced (information transduction) into hormones by the hypothalamus (limbic-hypothalamic-pituitary system) and released into the blood stream to communicate with the cells of the body. Learning, memory, stress, emotions and behavior are mediated by molecular messengers of the immune, endocrine, and autonomic systems (Rossi, 1993). In stage two, information important to environmental

adaptation carried by hormonal messengers influences expression of Immediate Early Genes (IEG's). IEG's are involved in memory and learning, and can also facilitate enduring adaptive physiological changes. Rossi (1998) proposed that IEG's play a key role in mind-body healing because they are involved in the simultaneous mediation of both psychological and biological levels. In stage three, gene translation leads to synthesis of new proteins. Production of proteins occurs in stages influenced by chronobiological rhythms with various proteins involved at different times subsequent to an event (e.g., within an hour, a few hours, or 12 or more hours). In stage four, messenger molecules pass through the blood-brain barrier and complete the loop of information transduction by influencing neural networks in the brain. In this way stress hormones, sex hormones, cytokines from the immune system, and other messenger molecules can influence the mind and emotions. Messenger molecules from the body are involved in encoding memory, learning, and behavior. These memories are state-dependent to physiological conditions associated with original encoding (state-dependent memory). Rossi proposed that the bi-directional influence between molecules of the body and mental experience is evidence that state-dependent memory, learning, and behavior is the "common denominator that bridges the mindbody gap" (p. 6).

The length of time for a complete cycle of mind-gene communication coincides with major 90-120 minute ultradian rhythms of cognitive-behavioral, genetic, and endocrine processes (Basic Rest-Activity Cycle, BRAC) (Rossi, 1994). Many psychological and holistic treatments, such as reiki, involve a 20 minute treatment period. Treatments involving relaxation, imagery, hypnosis, or physical stillness and rest likely entrain the 20 minute rest and relaxation phase of the BRAC. It is during this rest phase that our body rejuvenates and heals itself in preparation for the next activity phase.

Cerebral hemispheric dominance alternates with cycles of the 90-120 minute ultradian rhythm. During the 20 minute rest phase cerebral hemispheric activity may be more balanced. This may have implications for imagery therapies as raw imagery produced in the right hemisphere is transduced by the left hemisphere when there is good communication between the cerebral hemispheres (Rossi, 1993).

In summary, one's experience of the world (images, words, and emotions, etc.) is converted from neural impulses to physical form (messenger molecules). Cells, organs, and systems of the body receive this information from the central nervous system. IEG's respond to this chemical form of information and initiate protein synthesis as part of an adaptive response. Messenger molecules also communicate information from the body to the brain influencing the mind, emotions, learning, memory, and behavior. Many biological processes, including mind-gene communication, occur in rhythms 90-120 minutes in duration. This rhythm may be a key to both evoking and understanding mind-body healing processes.

Psychological Interventions

Psychological treatment of physical disease primarily involves the use of variants of relaxation, imagery, and hypnosis techniques. There is a certain degree of overlap between these approaches. In most cases they all involve a focusing of conscious attention, physical relaxation, and involvement of the senses in awareness of the body. Typically some form of mental imagery is incorporated into these treatments. While relaxation is considered a treatment in its own right, mental imagery is an essential component of most relaxation treatments. For example, patients may imagine a muscle lengthening as it relaxes or they may imagine themselves in relaxing settings (e.g., laying on a beach). As well, relaxation is typically used to prepare patients for imagery and hypnotic treatments.

What is referred to as hypnosis in many studies of immunomodulation is essentially deep physical relaxation and active mental imagery on the part of the subject. Some studies will use "hypnotic suggestion" where suggestions that the desired changes may occur are made while the subject in a relaxed state. In response, subjects may actively create images representing the suggestions or they may just passively listen to the suggestions. Although Comey and Kirsch (1999) found that intentional goal directed imagery was very common during hypnotic suggestions provided by an experimenter, researchers typically do not inquire about the cognitive experience of their research subjects during the treatment. Imagery techniques incorporate suggestions which are

usually visual and the patients choose or generate the imagery they will use to represent the immune changes. The cognitive processes involved in some hypnotic procedures may be very similar or the same as in a mental imagery procedure. All treatments involve a period when the patient remains physically still and enters in to a restful state. Hall (1982-83) noted that the imagery procedure used by Simonton et al. (1978) is functionally similar to hypnotic inductions.

Imagery and hypnosis have been used to treat a wide range of physical diseases or conditions. Imagery has reportedly been used in the treatment of arthritis and lupus (Rider, 1987; Rider & Kibler, 1990), pediatric migraine and headache (Annequine, Tournaire, & Massiou, 2000), pediatric acute pain (Golianu, Krane, Galloway, & Yaster, 2000), and tempomandibular joint syndrome (Gimbel, 1998). Hypnosis has been used for symptom control in irritable bowel syndrome, eosinophilic granulomatosis lung disease, sickle cell anemia, hemophilia, and chronic psychogenic cough (Hall, 1999). There is a large body of literature consisting of controlled studies and anecdotal reports that supports the contention that the mind can truly affect the body in many ways.

There is potential long-term benefit for patients who learn skills from imagery and relaxation treatments as the skills may be applied to other areas of life. Felt et al. (1998) found that 79% of children who learned relaxation-assisted immune imagery as at treatment for warts reported using relaxation and imagery in other areas of their life such as coping with stress or improving sports performance.

Despite positive findings of controlled trials and widespread use of imagery and hypnosis by health psychologists, these treatment have been largely rejected by physicians. The exception is in the treatment of fatal diseases such as cancer and HIV/AIDS.

Cancer

One modern application of imagery, known as the "Simonton method", has been used as a complementary treatment for cancer and other diseases since its development in 1971 (Simonton et al., 1978). In an uncontrolled study of 159 cancer patients with the prognosis of one year to live, Simonton et al. reportedly found increased longevity and cancer remission. Two years following diagnosis, 63 patients were still alive. Complete

remission and stabilization of cancer occurred in 22% and 27% of survivors respectively. The fact that the book describing the development and application of the technique (Simonton et al.) has sold over 1 million copies may attest to the widespread interest in imagery as a complementary treatment for cancer (Moore, 1995). Rossman (1984), and Zahourek (1988) describe variations of this technique.

Imagery is reportedly one of the mainstays of a 28-day psychoneuroimmunology and behavioural medicine program that involves a wide range of interventions such as stress management, group therapy, and nutrition education (Moore, 1998). Hall (1990) uses imagery of immune enhancement and cancer destruction as an example in his detailed protocol for the use of imagery in treating disease.

Gruber, Hall, Hersh, and Dubois (1988) treated 10 metastatic cancer patients using progressive muscle relaxation and instructions to imagine their immune system effectively destroying the cancer. There were significant elevations in several indicators of immune function compared with baseline: PHA Mitogen ($p < .02$), CON-A Mitogen ($p < .006$), Mixed Lymphocyte Response ($p < .03$), Interleukin-2 ($p < .03$), Natural Killer Cell Activity ($p < .001$), IgG ($p < .01$), and IgM ($p < .001$).

Relaxation training has also been found to provide immunological benefits for cancer patients. In a controlled study of the effect of relaxation training on immune parameters of patients receiving chemotherapy for ovarian cancer, relaxation training was associated with higher lymphocyte counts but not NK cell activity (Lekander, Furst, Rotstein, Hursti, & Fredrikson, 1997).

However, immune enhancement in cancer was not demonstrated in some controlled studies. Although the addition of immune enhancement imagery to standard chemotherapy for breast cancer significantly improved the quality of life ratings in the imagery group, clinical or pathological response to chemotherapy did not improve (Walker et al., 1999). Richardson et al. (1997) randomly assigned 47 women to 3 groups. Two groups received psychological interventions, either weekly support groups or immune enhancement imagery training in addition to standard medical care. A control group received medical care only. After six weeks, the groups did not significantly differ on several measures of immune function. Social support and coping skills improved with

both interventions. Compared to the support group, the imagery group reported less stress, and improved functional and social quality of life.

Spiegel & Moore (1997) concluded in their review of imagery and hypnosis that hypnosis is effective for controlling pain, but there is no reliable evidence that immune enhancement imagery affects disease progression or survival. Other reviews also supported the use of imagery to manage pain in cancer patients (Chang, 1999; Wallace, 1997). Breast cancer patients experienced significant increases in comfort during radiation therapy from practicing guided imagery with the aid of audiotapes (Kolcaba & Fox, 1999). Although nausea and vomiting did not decrease for chemotherapy patients who received guided imagery treatment, responses on The Chemotherapy Experience Survey revealed that their overall perception of chemotherapy was more positive than a control group (Troesch, Rodehaver, Delaney, & Yanes, 1993).

A variety of training programs for health professional are available, including a Nurses Certificate Program in Interactive Imagery (Ezra, 1997). An Australian study of general practitioners found that 34% had trained in mediation and 20% had learned hypnosis techniques (Pirotta, Cohen, Kotsirilos, & Farish, 2000). Chiaramonte (1997) advocated that imagery, as well as relaxation, and meditation can be a useful adjunct for the primary care physician in treatment disease such as cancer, HIV, and hypertension. Learning how to use imagery to influence the course of their disease or even decrease symptoms is empowering for patients (Chiaramonte). Zaza, Sellick, Willan, Reyno, and Bowman (1999) conducted a survey of health care professions at two cancer treatment centres in Ontario, Canada to assess non-pharmaceutical recommendations that are provided to cancer patients for pain management. The 141 respondents most commonly recommended support groups (67%), imagery (54%), music/art therapy (49%), and meditation (43%).

Adjunct psychological treatments are becoming more accepted in diseases such as cancer and HIV. In a study of Australian children with cancer (N=48), it was revealed that 15% had tried mental imagery therapy and 15% used hypnotherapy (Colman, 1994). Unfortunately, many cancer patient seek out adjunct psychological treatments and do not inform their physicians.

HIV

Evidence of the immunosuppressive effects of stress led researchers to examine the effects of relaxation and stress management effects on HIV-positive and AIDS patients. Solomon (1987) called for research in the area of HIV to include studies of personality factors associated with longevity, stress related effects, and efficacy of behavioral interventions such as relaxation and hypnosis to enhance immune function, among others.

A 10-week study examined the effects of relaxation on mood and immune parameters of symptomatic HIV-seropositive gay men compared a wait-list control group (Lutgendorf et al., 1997). Patients who practiced relaxation had significant decreases in herpes simplex virus-Type 2 immunoglobulin G antibody titers, and self-reported levels of anxiety, dysphoria, and total distress. Following progressive muscle relaxation, HIV-seropositive patients without AIDS had significant decreases in anxiety, fatigue, depression and confusion compared to two control conditions (supportive psychotherapy group and no psychological treatment) (Fukinishi, 1997).

No significant changes in CD4+ T-lymphocytes were found in HIV-positive men following 6 weeks of progressive muscle relaxation (McCain, Zeller, Cella, Urbanski, & Novak, 1996). However, relaxation was associated with increased emotional well-being. Results from a 6-month follow-up revealed that relaxation was associated with a decrease in HIV-related intrusive thinking.

Ostrow et al. (1997) surveyed use of complementary therapy among patients of a Vancouver HIV/AIDS drug program. Mental relaxation techniques had been used by 20% of the 657 patients who responded to the survey. Green et al. (1999) reviewed the current state of peer-reviewed evidence of complementary treatments for AIDS indexed in MedLine and concluded that despite frequent use of these approaches little clinical research is reported on MedLine.

Psychological Interventions for Asthma

Only in the last 10-15 years has the importance of the inflammatory component of asthma been elucidated. When most of the studies of psychological treatments of asthma were conducted, the importance of inflammation was not fully appreciated, and

bronchoconstriction was considered the primary feature. Asthma was considered a psychosomatic disorder originating from factors such as personality, emotional stress, anxiety, physical tension, and family dynamics. Proposed psychological treatments included relaxation training, systematic desensitization, psychotherapy, cognitive therapy, hypnosis, and family therapy (Lask, 1991). Anecdotal reports on the use of psychological interventions in the treatment of asthma are numerous and include: imagery and relaxation (Mendelberg, 1990), psychotherapy (Erickson, 1977b), and therapeutic metaphors (Kershaw, 1987).

Treatment of asthma with hypnosis has been associated with improvements in forced vital capacity, peak flow, and symptoms in children experiencing asthma attacks (Aronoff, Aronoff, & Peck, 1975). Some individuals with asthma react to non-hypnotic suggestions of bronchoconstriction and bronchodilation with directional changes in mean forced expiratory flow between 25% and 75% of the expired vital capacity ($FEF_{25-75\%}$), but not forced expiratory volume in 1 second (FEV_1) (Isenberg, Lehrer, & Hochron, 1992).

Brown and Fromm (1988) conducted an extensive review of psychological treatments of asthma and concluded that direct hypnotic suggestions are not useful and typically do not result in increased pulmonary function. White (1961) found that hypnotic suggestions of symptom relief may result in decreased perception of symptoms in absence of, or despite decreases, in pulmonary function. Unfortunately, this study was limited in terms of outcome measures and improvements in pulmonary function may have gone undetected.

In a recent review of complementary treatments for asthma, Ziment and Tashkin (2000) speculated that hypnotism, biofeedback, and other similar treatments improve autonomic balances that occur in diseases such as asthma. As well, although they do not provide an extensive review of studies, they conclude that positive imagery representing physiological changes can lead to measurable benefit in asthma. Another recent review of complementary therapies for asthma mentions psychological treatments in the introduction to the article but fails to include them in the extensive review of other

treatments which include: nutrition, herbs, homeopathy, and acupuncture (Hackman, Stern, & Gershwin, 1999).

Studies examining relaxation training as a treatment for asthma have produced mixed results. Relaxation techniques involving a mental component such as autogenic training, biofeedback, or systematic desensitization were found to be associated with clinically significant improvements in lung function, while muscle relaxation alone appeared to be ineffective (Erskine-Milliss & Schonell, 1981). Of subjects with asthma who received relaxation training combining progressive relaxation, systematic desensitization, and biofeedback, only those with large airway obstruction demonstrated a short-term improvement measured by a methacholine challenge test (Lehrer et al., 1986). Philipp, Wilde, and Day (1972) found relaxation and breathing exercises decreased airway reactivity to a methacholine challenge test compared to controls, but did not assess type of airway obstruction. In children with mild to moderate asthma, relaxation induced by tensing then relaxing muscles did not improve the treatment efficacy of an asthma self-management program compared to controls (Vasquez & Buceta, 1993). Lehrer (1998) reviewed studies on the contribution of panic disorder to asthma symptoms. Noting positive findings in preliminary research on biofeedback as a treatment for asthma, Lehrer hypothesized that relaxation treatments will be of most benefit to asthma patients who experience panic symptoms.

Reviews of studies conducted on psychological treatments for asthma generally conclude that some supportive evidence exists, but further research is necessary (Cluss & Fireman, 1985; Lehrer, Sargunaraj, & Hochron, 1992; Lane & Lane, 1991). Numerous methodological flaws in many of the studies preventing strong conclusions of treatment efficacy (Cluss & Fireman, 1985; Mrazek & Klinnert, 1991). In many studies, treatment effects may have been undetected due to limited use of spirometry, and lack of symptom or peak flow diaries. Recognizing that many people with asthma turn to complementary treatments despite limited research on the therapies, the National Institutes of Health established a Center for Alternative/Complementary Medicine in Asthma and Allergies at the University of California at Davis (Gershwin, 1997).

Imagery Treatment Protocols

What is Imagery?

To provide a context for the treatment protocol developed in Zukiwski (1996), I will explain what imagery is and review the approaches to imagery treatment used in research as well as clinical practice.

"Imagery" refers to mental representations that can incorporate any or all of our senses. Images may be created using vision, sound, taste, smell, touch, the sensation of movement, and inner sensation (Achterberg, Dossey, & Kolkmeier, 1994). Imagery does not occur only in a therapy session, as all thought requires some form of imagery. Negative images related to disease processes or treatment efficacy may negatively affect patient progress. Patients worrying about their disease outcome are likely to imagine the disease state rather than recovery or wellness (Rossman, 1984).

Marks (1999) distinguishes between two forms of mental imagery. One form is conscious and can be subjectively described in terms of vividness, color, etc. The other is not accessible in consciousness and is used in processing information (e.g., when performing perceptual tasks). Marks proposed that imagery is a basic-building block of consciousness.

Imagery may increase the effectiveness of psychological treatments. A common imagery technique involves the imagining of a place or situation that the patient would find calm and relaxing. The "calm scene" imagery is usually preceded by a progressive relaxation induction. de L. Horne, Taylor, and Varigos (1999) found that progressive muscle relaxation is more effective when relaxation imagery is included. In a small controlled study with eczema patients, progressive muscle relaxation combined with a relaxing image resulted in significantly greater reductions in ratings of self-reported itchiness than progressive relaxation alone.

Research Protocols

One difficulty in comparing the results of immunomodulation studies is the variety of treatment methods used. For example, while many studies refer to the treatment as hypnotic, the actual treatment can vary greatly. Some studies use hypnotic suggestions without requesting active cognitive involvement of the participants. In these

cases the subjects may passively listen to the hypnotic instructions or they may actively imagine the changes actually occurring. Other studies request active cognitive involvement by asking the subject to vividly imagine the desired changes during the "hypnotic" treatment (Spanos, Stenstrom, & Johnston, 1988).

Unfortunately, the majority of published descriptions of the studies of intentional immunomodulation contain only limited descriptions of what was actually done during the experimental sessions.

Example of research protocol

Rider and Achterberg (1989) utilized audiocassette tapes during training and intervention sessions as well as home practice. The taped induction consisted of a 10 min Jacobsonian progressive relaxation procedure with background music, a 1 min period of imagery instructions, and a final 10 min of specially composed music. Two preliminary sessions involved training in progressive muscle relaxation and "endogenous imagery on the morphology and location" of neutrophils or lymphocytes (depending on the group) (p. 251). Imagery was enhanced by having the subjects draw the images with crayons and then discuss it. The subjects were then instructed to practice the imagery several times a week for the next 6 weeks. Pre- and post imagery blood samples were taken in a final testing session.

Rider and Achterberg (1989) describe the instructions provided to each of the two groups:

> (Instructions to the neutrophil group)...centered on the morphology of neutrophils and their location and movement within the body. Subjects were taught to focus on the flexible shape of the cells and the segmented neclei (sic) that are uniquely characteristic of neutrophils. Subjects were also instructed to image the mature neutrophils leaving the bone marrow of the thoracic skeletal system through capillaries in the ends of the bones and entering the vasculature...(Subjects instructed to influence lymphocytes)...were taught that lymphocytes were round cells with a single large nucleus. Subjects were instructed to image the mature lymphocytes leaving lymphatic structures, such as the thymus, spleen, and lymph nodes, and entering the vasculature through the subclavian vein. (p. 252)

Both groups were provided with information on how each cell reacts to foreign matter, such as the process of phagocytosis, but were asked not to focus on this activity during imaging.

Few studies on intentional immunomodulation provide sufficient information to permit accurate replication or facilitate comparison with other studies. The script from Rider and Achterberg (1989) presented above is a glaring exception. Another exception is Hall (1990) who provided a detailed protocol that can be used for both research and clinical practice.

Components of Imagery Treatment

A brief overview of the components of imagery treatment was provided in Zukiwski (1996). A more detailed comparison of imagery treatments used in research and clinical practice will be provided here. Some of the components, such as the use of an induction to facilitate relaxation, education, and home practice relate to the structure of the treatment. Others, such as imagery characteristics, may relate to the effectiveness of the imagery.

Induction

The use of an induction is virtually unquestioned in the literature. Norris (1989) stated: "We have found that a quiet body, quiet emotions, and a quiet mind constitute the physiologic state that is most conducive for visualization" (p. 61).

Progressive relaxation is commonly used either solely or as part of an induction. Rossman (1984) used an audiocassette to teach progressive relaxation to his patients prior to using imagery. He first instructs his patients to listen to a 22 min relaxation induction. Once they are proficient, they can then use a 10 min induction that is followed by two deepening techniques, one utilizing a 1-10 count, and the other uses imagery of a beautiful and relaxing place. The relaxing imagery is used to lead into therapeutic imagery. Rossman reports that relaxation alone may produce relief in stress-related atopic disorders such as asthma, eczema, and hay fever.

Hall (1990) provided a script of his induction that incorporates relaxation, suggestions, and elicitation of classic hypnotic phenomena. The induction protocol

begins with the subject sitting with arms and legs uncrossed, and eyes closed. A passive progressive relaxation induction is followed by the subjects "calm scene" imagery. Further deepening is accomplished, first, by a 1-20 count combined with suggested imagery of a floating cloud or an elevator going down during the count, then, by instructions to extend an arm and imagine it being pulled down by a heavy weight. The subject is then instructed to imagine the desired immune system changes and is allowed approximately 5 min to imagine the changes without further instruction. The subject is reoriented using a 10-1 count, and is questioned about their experience. The induction protocol "is geared toward creating a psychological ritual that everyone can experience" (p. 215).

Achterberg et al. (1994) suggested that music can be helpful in promoting relaxation and evoking imagery. Although music was used to assist imagery practice in the immunomodulation research conducted by Rider and Weldin (1990) and Rider and Achterberg (1989), the majority of researchers in this area have not used music as part of an induction. Music does not appear to be necessary, and in research it could serve as an additional variable.

A study by Spanos et al. (1988) provides some evidence that an induction may not be necessary. Subjects who listened to a hypnotic induction prior to hypnotic suggestions to imagine wart regression were equally likely to have wart regression as those who only received hypnotic suggestions. Self-reported ratings of relaxation or hypnotic alteration of experience were not related to wart regression.

Length of Treatment Session

Although there is a wide variety of treatment session length in the literature, most are approximately 20 to 30 minutes in length. Achterberg et al. (1994) stated that home practice of an imagery treatment takes approximately 20 minutes. Spanos et al. (1990) used a 10 min hypnotic induction and 2 min of suggestions of wart regression. Hall et al. (1992) utilized a 30 min treatment session.

Rossi (1993) noted that a common element to many mind-body techniques is a 20 minute period of treatment. Rossi advocated that patients take frequent 20 minute rest breaks to facilitate the Ultradian Healing Response, which is advocated as a treatment of

psychosomatic disease (Rossi, 1991). Many studies control for the factor of a period of rest by incorporating an alternative treatment or placebo condition.

Pretreatment Imagery and Drawing

Mental representation of the pre-treatment disease state or current treatments is often elicited in clinical practice (Achterberg et al., 1994; Siegel, 1986). Drawings of the disease state imagery may be useful in assessing clinical prognosis (Achterberg & Lawless, 1984; Siegel 1986) and may be used to address fears or misunderstandings about the disease and/or treatment (Norris, 1989).

Siegel (1986) asked all new patients to draw pictures of themselves, their treatment, disease, and white blood cells eliminating their disease. He reportedly found the drawings to be accurate aids in determining the patient's prognosis. When a patient worries about the prognosis of their disease, they are likely imagining a decline in their health. Alternatively, when patients have hope, they are likely imagining a more positive outcome. Imagery representing poor disease outcome may act as a form of autosuggestion (Rossman, 1984). Support for this hypothesis is provided by the research on the relationship between imagery and cancer prognosis (Achterberg & Lawlis, 1984).

Both researchers and clinicians have observed that imagery representing ineffective treatment or a lack of belief in the treatment, tended to indicate a poor prognosis, while images of successful treatment tend to indicate better prognosis (Simonton et al., 1978; Achterberg & Lawlis, 1984).

Drawing of treatment imagery may assist the clinician or researcher in gaining a more thorough understanding of the process that the patient is imagining. This provides an opportunity for feedback and may reveal errors in the imagery that patients created. As well, drawing the imagery may increase the vividness of visual imagery and the intensity of the other senses (Achterberg et al., 1994). Thus, patients who have difficulty producing visual imagery may benefit from drawing the images.

With the exception of a study on the effect of imagery on neutrophils and lymphocytes (Rider & Achterberg, 1989), drawing has not been included in immunomodulation studies.

Education and Imagery Development.

While most imagery treatments designed to alter specific parameters of immune function incorporate education about the immune system, many hypnotic treatments do not. The issue of how much education is necessary or optimum has not been addressed in the literature. Do patients need only a brief description of the relevant aspects of the immune system or physiology? Is an in-depth description more effective, or is education not needed at all? Unfortunately, most studies and anecdotal reports do not provide detailed descriptions of education procedures.

The education component of Hall's (1984) protocol is very brief. In the case of treating a cancer patient, Hall provided the following statements:

> There's a subpopulation of white blood cells, or lymphocytes, which become active in the presence of a foreign substance or cancers. This subpopulation of cells directly attack the foreign agent like sharks attacking meat or pacman eating its foes. Provide your own description of these cells. (p. 218)

In medical hypnosis, patients are typically not provided education about the underlying disease process. Instead, hypnotic suggestions are just given and it is presumed that the unconscious mind has the wisdom to make the desired changes. For example, hypnosis has been used in the treatment of wart in both clinical practice and research. I am not aware of any study involving hypnotic treatment of warts that involved an educational component. This is also the case in studies on the effect of hypnotic suggestions on immediate or delayed hypersensitivity reactions (e.g., Smith et al., 1985).

Another consideration in developing a treatment protocol is how the education be provided. Should a description of immune cell function be presented verbally or with the aid of illustrations or photographs? Lack of research data or anecdotal reports on this issue prevents any conclusions. I speculate that some patients may benefit from visual aids, while others may be less creative in generating their own imagery after viewing a concrete representation of immune function (e.g., a photograph of a mast cell releasing histamine and other mediators).

Home Practice

In some studies the effects of imagery or suggestion are examined only within one or two sessions, no home practice or extended training is included (Jasnoski & Kugler; Johnson & Barber, 1976; Olness, Culbert, & Uden, 1989; Rider & Weldin, 1990). Other studies require home practice of the imagery treatment (e.g., Locke, et al., 1987; Spanos et al., 1990; Rider & Achterberg, 1989). In clinical settings home practice is always recommended (e.g., Norris, 1989; Achterberg et al., 1994).

Regular and frequent practice is a common factor reported by therapists reporting success with imagery (Rossman, 1984). If the condition is life threatening it may be beneficial to practice the intervention two or three times daily, as well as briefly evoking the imagery numerous times per day (Achterberg et al., 1994).

In research, home practice varies widely in length of time, and number of times per day. Audio taped scripts are sometimes used, but frequently the length of the tape, or a description of the script is not provided. Spanos et al. (1990) instructed their research participants to practice each day imagining the warts receding for 1 min per wart-infected limb. No induction was used prior to daily practice. Other attempts at successful home practice include: 5 audiotape assisted practice sessions in 2 days (Locke et al., 1987); 30 min per day, no audiotape (Hall et al., 1992); 30 min twice each day without audio tape, but with printed instructions on how to relax first (Hall, 1990); practice several times weekly for 6 weeks using an audiotape (Rider & Achterberg, 1989). To my knowledge, there have been no systematic comparisons of home practice protocols in immunomodulation research.

Characteristics of Treatment Imagery

Ideosyncratic. In descriptions of clinical practice and research, the importance of patient or participant created imagery is frequently stressed. When the individual patient creates their own imagery based on the education provided by the researcher or clinician, it is more likely to be consistent with their personal experience, knowledge, and metacognitive processes. Norris (1989) emphasized that imagery must be designed by the individual patient, "utilizing internal symbology that has deep, unconscious, personally unique meanings" (p. 62).

Norris (1989) reported that effective imagery must be consistent with the patient's values and goals. The image should have the sensation that it is taking place within the body. This is facilitated by including kinesthetic as well as other sensory modalities.

Accuracy. The imagery created by the participant must contain an anatomically correct symbolic or realistic representation of the desired changes (Norris, 1989). Norris reported that attempts to make imagery too scientifically or technically accurate may lead to feelings of frustration or helplessness. Symbolic imagery is reportedly more powerful and effective than concrete imagery. Rider and Kibler (1990) found that imagery had a tendency to change from concrete to more symbolic and complex.

Whether symbolic or concrete, the patient generated imagery should accurately represent the desired immune system changes. The clinician or research should provide feedback and suggest corrections to make the imagery more accurate. Hall (1990) allowed for correction of imagery in his protocol.

Simonton et al. (1978) found that imagery tends to be more effective when it accurately reflects the desired physiological changes. They recommend that cancer patients should represent their white blood cells, or their treatment, such as radiation therapy, as more powerful and more numerous than the cancer cells. The imagery should also include: removal of the defeated cancer cells from the body, recovery of the normal tissues that may have been damaged, and images of being healthy and achieving life goals in the future.

Vividness. The common sense conclusion that vivid imagery would likely be more powerful than flat and colorless images is supported by clinical experience and research findings. Spanos et al. (1988) asked their "hypnotic" treatment group to "vividly imagine their warts shrinking and dissolving away" during the treatment session and in home practice (p. 248). Vividness of visual imagery was significantly corrected with wart regression, yet there was no correlation between wart regression and the results of the Betts vividness of imagery questionnaire or a hypnotizability test.

Bandler (1985) provided a thorough explanation of imagery characteristics and the clinical effects of altering them. For example, a visual image may be coded in black-and-white or color. A visual mental image can be described in terms of vividness, brightness,

size, dimensionality, spatial location, etc. Most patients can readily alter these characteristics of a visual image.

Other Clinical Issues in Imagery Treatment

A few additional issues are worthy of mention. The issues of secondary gain, belief, and dialogue with imagery are discussed in the clinical literature but are not addressed in imagery research.

Secondary Gain & Resistance

Physical illness may produce secondary gains for some individuals. If the secondary gain is significant, there may be conscious or unconscious resistance to recovering from the condition. As an example of secondary gains, Dilts, Hallbom, and Smith (1990) used the example of a child that receives considerable attention as a result of allergies or asthma. It may be important in such a case to find alternative ways that the child could get the attention.

Barnett (1989) contended that when direct hypnotic suggestion provides only temporary relief of symptoms, "it may well be that the unconscious motivation for recovery is poor or absent resulting in reduced mobilisation (sic) of available unconscious resources...there may persist an unconscious wish for self destruction inevitably increasing the likelihood of continued or increasing disability" (p. 445).

Many individuals may not be consciously aware of secondary gains associated with their illness. It may be beneficial in clinical and even research settings to ask patients if they are aware of any benefits related to having the illness and if any negative changes in their life may arise if they get better.

Expectancy

Belief appears to play a role in the efficacy of imagery treatment. In a review of interventions used to influence immune function, Hall and O'Grady (1991) concluded that the "therapeutic effects of psychosocial intervention are, in most instances, dependent on a strong belief on the part of the subject that the intervention is going to have a beneficial outcome" (p. 1076). Achterberg et al. (1994) emphasized that a positive expectancy is a

crucial component of imagery healing techniques but do not elaborate on how to develop it.

Spanos et al. (1988) assessed the effect of expectancy in their study on hypnosis/imagery and wart regression. Subjects who had wart regression were equally likely as to those who did not, to hold high expectations for treatment success. None of the subjects with very low expectations experienced wart regression. Spanos et al. concluded that wart regression is likely to occur only in subjects with moderate-to-high expectations of treatment success.

Dilts et al. (1990) reported that client held beliefs appear to be able to interfere with desired changes, despite otherwise successfully completed psychological change techniques: "if people really believe they can't do something, they're going to find an unconscious way to keep the change from occurring" (p. 3).

Considering the potential impact of this patient variable, it should be examined further. Clinicians and researchers can easily inquire if patients believe the treatment will work, and if they have any prior experience mind-body treatments.

Dialogue. Some imagery and hypnotic treatments involve establishing an inner mental "dialogue". Rossman (1984) asserted that a valuable technique is to facilitate the patient to imagine an "inner advisor". In a relaxed state, the patients are encouraged to allow an image to form that represents wisdom and caring. The image may be a visual representation of a human, animal, or other symbol, or it may be represented in another sensory modality, such as a feeling (kinesthetic). A dialogue is established, and the inner advisor is asked questions about the patient's illness. Patients also develop images representing the symptom or disease and establish a dialogue to reveal what is needed to improve their health. The process of accessing then dialoging with the problem image is similar to hypnotic techniques, such as Rossi's (1993) "converting a symptom into a signal" (p. 271).

In research studies on immunomodulation, dialogue is not typically incorporated into imagery treatments that target specific immunological changes. While dialogue may be a useful clinical addition, imagery researchers should continue to examine the

hypothesis that imagery alone can be used to cause specific changes in the immune system.

Summary

This study is designed to examine the hypothesis: adults with moderate asthma who are trained in, and practice, using relaxation-assisted imagery representing desirable functional and cellular changes in the lungs will show improvement in lung function more than those who receive the same degree of education about asthma, but are trained in, and practice, using relaxation-assisted "calm scene" imagery. The aim of the study is two fold. First, to evaluate in a randomized controlled clinical trial, the efficacy of the asthma imagery treatment protocol developed in a previous study (Zukiwski, 1996). Second, to isolate the effect of immune specific imagery by controlling for a multitude of treatment factors common to psychological treatments that incorporate mental imagery.

I expect the outcome of the study to be consistent with anecdotal results of previous case studies in Zukiwski (1996); lung function and symptoms will improve. (Zukiwski, 1996). However, improvement may be seen in different measures of lung function. Some patients may improve in FEV_1, while others may improve in FVC or FEF_{25-75} (or a combination of these measures). This will dramatically reduce the likelihood of obtaining a statistically significant result. The goal of isolating type of imagery resulted in a study design that compares two almost identical treatments. The relaxation imagery treatment will likely have some beneficial effect on lung function and symptoms. Considering the small sample size (low power) and lack of a no-treatment control group, if some degree of improvement is expected with both treatments, it is unlikely the difference in treatment efficacy will reach statistical significance.

While reducing the likelihood of a statistically significant result, the study design improves the meaning and importance of significant results. A statistically significant result may support the primary presupposition of an imagery based psychological technique that is currently used as a treatment for a wide range of physical disorders: autonomic physiological processes, such as immune function, are susceptible to influence with the intentional practice of mental imagery representing desirable changes in those autonomic processes.

Significant results in this study would support further research on the use of imagery as an adjunct treatment for asthma, and possibly other immune related disorders. Clinically significant results would likely support the wide spread use of this treatment in conjunction with pharmacological treatments currently available.

CHAPTER 3: METHOD AND PROCEDURES

Method

Design

This was an 8-week randomized, single-blinded, controlled, two group, and true experimental study. Primary efficacy outcome measures were obtained from pre- and post-treatment spirometry. Secondary efficacy measures included daily home measurements of peak expiratory flow, symptoms, and medication usage.

The protocol for this study was approved by the Research and Ethics Committee of the Department of Educational Psychology, University of Alberta, and the Research Steering Committee of the Caritas Health Group.

This research was supported by an operating grant from the Caritas Research Steering Committee and non-monetary support from the Alberta Asthma Centre and the University of Alberta Pulmonary Research Group.

Patient Population

Unpaid volunteers with moderate to severe asthma were recruited through asthma clinics in two area hospitals, primary care physicians, and public advertising (fliers, newspaper ads, and public service announcements). Recruiting from multiple sources may provide a more heterogeneous sample of asthma patients. Abdulwadud & Abramson (1999) found significant differences between hospital clinic and general practice patients in terms of education level, severity of asthma, use of theophylline, presence of exercise limitation and number of hospital admissions.

Over 330 potential volunteers who responded to public advertising were pre-screened by telephone to determine eligibility. When available, records of previous spirometric assessments were requested from volunteers' physicians. An unknown number of patients attending hospital asthma clinics were screened by cooperating pulmonologists, respiratory therapists, and the researcher to determine eligibility. Patients who met inclusion criteria were informed about the study. If they expressed interest, they were invited to contact the researcher. Recruiting, assignment to groups, and provision of treatment was conducted on an ongoing basis.

Twenty-six volunteers were recruited for participation in this study. This included 18 females and 8 males between the ages of 19 and 64 with a mean age of 46. Severity of asthma as indicated by percent of predicted forced expiratory volume in one second (FEV_1) was between 34 and 79 percent with a mean of 59.2 percent. Participant demographics before and after attrition will be presented in the results section.

All subjects met the following criteria: (a) current or prior diagnosis of bronchial asthma established, in part, by a significant reversibility of FEV_1 following inhalation of bronchodilator (≥15% or ≥12% with a change in volume of at least 180 mL.); (b) age between 18 and 70; (c) $FEV_1 \leq 80\%$ of their predicted value; (d) on a stable preventative regimen involving inhaled anti-inflammatory medication for a minimum of 6 weeks prior to the study; (e) non-smoker for at least 12 months; (f) absence of infectious disease. Exclusion criteria included: (a) smoking within the past 12 months, (b) diagnosis of co-morbid lung diseases, (c) abnormal diffusing capacity, (d) pregnancy, (e) recent surgery, and (f) severe health problems, other than asthma, that may affect the immune or endocrine systems. Volunteers were excluded or entered into the study at a later date if any of the any of the following occurred in the 6 weeks preceding involvement in the study: (a) use of oral steroids; (b) asthma related hospital admission; or (c) respiratory infection. Participants were allowed to use inhaled short-acting bronchodilators as needed for breakthrough asthma symptoms. Patients were also permitted to use medication for allergy and rhinitis such as antihistamines or intranasal corticosteroids.

All potential volunteers who reported prior experience with imagery or hypnotic treatments were excluded. As well, volunteers who reported using relaxation techniques to manage their asthma were excluded. Recent or concurrent use of other complementary treatments such as chiropractic or acupuncture was not permitted. Exercise, herb, and vitamin use were permitted only if their use was well established and were not altered during the study.

Written and verbal explanation of study details was provided to volunteers (Patient Information Sheet, Appendix A). Informed consent was obtained from all participants (Appendix B).

Measurements

Spirometry. Assessments of lung function were performed using calibrated computerized spirometers (Cybermedic Spinnaker TL spirometer, Colorado; Sensormedics 2130 spirometer, California) according to American Thoracic Society (ATS) (1987) criteria in the pulmonary labs of two area hospitals by qualified technicians or respiratory therapists. Spirometry was conducted between 11:00 AM and 2:00 PM to control for diurnal variations. At the outset of the study three tests were performed: (a) a flow volume loop (FVL), (b) total lung capacity (TLC), (b) and airway resistance (R_{aw}). However, during the study an independent expert recommended the following changes in data collection: (a) discontinue assessment of TLC for reasons of budget and relative unimportance in data analysis, and (b) discontinue assessment of R_{aw} due to unreliable data obtained from a body plethysmograph.

Bronchodilator medications were withheld prior to spirometric assessment (e.g., β_2 agonists for 8 hours, long-acting bronchodilators for 12 hours, short-acting theophyllines for 12 hours, and long-acting theophyllines for 24 hours). Depending on the time of regular medication use, some participants withheld for longer periods. They were instructed to record the time between last dose and spirometry for accurate replication of withhold durations for post-treat spirometry.

Two flow-volume loops (FVL), separated by 2 metered inhaled doses of a bronchodilator (Ventolin) and a 10 minute waiting period, assessed reversibility of bronchoconstriction. Outcome measurements obtained by spirometry included: FEV_1, FVC, peak expiratory flow rate (PEFR), and $FEF_{25-75\%}$. FEV_1 has very good reproducibility and is the best pulmonary function variable for monitoring airways obstruction (Enright et al., 1994). Predicted values for FEV_1 were calculated according to norms from Morris (1976).

Asthma Diary

Peak expiratory flow rates (PEF), asthma symptoms and their severity, medication usage, and frequency of practicing the intervention were recorded in a diary on a daily basis (Appendix C).

Peak flow. Peak expiratory flow (PEF) was measured at home using a Mini-Wright Peak Flow Meter (MPFM) (Clement Clarke Inc., Columbus, Ohio). Verbal and written instructions in the proper use of the MPFM were provided at the time of initial spirometry. The best result of 3 efforts was recorded on the diary in the early morning (AM) and evening (PM) at approximately the same time each day (± 30 minutes). Participants were advised to obtain PEF measurements immediately before morning and evening doses of medication.

Symptoms. Self-ratings of symptom severity were recorded in the evening each day using a scale from 0 to 5 (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe, 5 = required medical attention). Symptoms included: morning wheeze, daytime wheeze, dry cough, cough with expectoration, shortness of breath, chest tightness or discomfort, night or early morning waking, and "had to take a rest", and sensitivity to inhaled irritants. Symptoms were evaluated separately for each symptom category. This diary is the same as used in Zukiwski (1996) with two exceptions. A 0 to 4 scale was used in this initial study. A participant in that study stated they were reluctant to select the 4-point category, as "very severe" to them would mean treatment at an emergency room (which was an exclusionary criteria). In effect, this patient evaluated all symptoms on a 0 to 3 scale, limiting the range of possible responses. Based on this feedback, the symptom rating scale was expanded to 0 to 5. In making the decision to add this category, I expected that it would not be used. In the event it was used, that participant would likely be excluded from the study. Anecdotal reports of decreased sensitivity to inhaled irritants in the Zukiwski (1996) prompted the addition of a new symptom category to assess these changes. Participants also recorded daily medication usage and frequency of home practice of the treatment.

Procedures

Treatment Compliance

Poor compliance is a factor that decreases the effectiveness of pharmaceutical treatment and is a significant concern in research. Inhaled corticosteroids are commonly self-administered twice each day. Compliance with self-administration of medication is crucial to suppressing the inflammatory components of asthma. Patient compliance with medication is affected by at least 4 general types of factors: patient variables, nature of asthma, medication characteristics, and interactions with physicians and medical staff (Creer & Levstek, 1996). Creer & Levstek conclude that incomplete or inadequate instruction is the major determinant of inhaled medication compliance. Patients who use their medication very infrequently may forget how to administer it properly. Bad medication administration habits may develop among those who take medication regularly. Creer & Levstek recommend monitoring of patient's inhaler technique.

Inhaler technique was not monitored or corrected in this study. Correction of inhaler technique might have improved medication delivery and thus constituted a confounding variable.

Home monitoring of PEF is a common component of treatment and clinical trials. Self-report PEF data is limited by participant honesty and motivation. Evidence in the literature of non-compliance with daily measurements of PEF suggests limited validity of diary data. From the outset of a 1-year study in which participants measured PEF daily and adjusted medication according to an action plan, thirty percent of patients (8 of 26 subjects) never or only infrequently measured their PEF (<25% of measurements completed) (Cote, Cartier, Malo, Rouleau, & Boulet, 1998). Seven of these patients fabricated results most of the time. Despite regular reinforcement of the importance of measuring PEF on a daily basis, average compliance fell from 63% during the initial month to 51% at 6 months. At 12 months, 16 of 26 patients fabricated results.

To address the issue of compliance with collecting diary data, participants were strongly encouraged to be honest in their reporting. They were informed that statistical methods could be used to address missing data but that fabricated data could damage the

study. Participants were requested to bring their diary to each treatment session for review.

Informed Consent and Randomization

Potential volunteers contacted the researcher by phone after initial exposure to the study through advertising or referral. They were informed of the nature of the study with emphasis that the goal of the study was to examine two psychological treatments to determine if they differ in effectiveness. They were told that neither of the treatments is a placebo condition. The volunteers were asked to provide a wide range of information to determine eligibility, including: medication usage, recent medication changes, use of oral anti-inflammatories, smoking history, history of asthma diagnosis, symptoms, asthma exacerbations, allergies, recent illness or surgery, pregnancy, use of complementary treatments, prior research experience, and scheduled vacations. If exclusion criteria were met, no further questions were asked. Thus, complete responses are not available.

Eligible volunteers were provided with a detailed written explanation of the study (see Patient Information Sheet, Appendix A). Volunteers were scheduled for spirometry to confirm their eligibility to participate and provide pre-treatment data. During this assessment, asthma diaries and PFM's were provided along with verbal and written instructions in their use.

Participants were then individually randomly assigned into either an experimental group (group A) or a referent group (group B) according to a randomization schedule generated by a statistician for this study.

Blinding Procedures

Respiratory therapists, technicians, physicians, and all staff that had contact with participants were blinded as to group assignment. Participants were not informed about the types of imagery treatment being compared in the study until the first treatment session. At that time they were only informed about the nature of their respective treatment. Unlike studies incorporating placebos in which patients do not know whether they are receiving an active treatment or placebo, in this study all participants knew they were receiving an active treatment. Participants were told that if the results of the study

indicated that the other treatment was more effective than the one they were learning, then they would have the opportunity to learn about it after the conclusion of the study.

Training of Research Assistants

It became necessary to train research assistants (RA) to ensure the study would be completed within the desired time period. Approximately half way through the study a senior research assistant (SRA) was hired to assist in administering treatments to both groups. The SRA was a doctoral level graduate student in counselling psychology with experience in health psychology. Training provided to the SRA for this study consisted of directed readings on relevant immunology, review of research protocols, and one-on-one tutoring. On several occasions the SRA directly observed complete treatment sessions administered by myself. When the SRA was familiar with both treatments and had a working knowledge of asthma pathophysiology, she began administering treatments. Ongoing supervision was provided in the form of review of case notes and in-person or telephone consults. Later, two additional doctoral level graduate students in counselling psychology were recruited to serve as research assistants (RA). The SRA assisted in training and ongoing supervision. In addition to reviewing research protocols, all RA's attended a full day training in-service. I provided a detailed review of necessary background knowledge and treatment procedures. Two highly motivated asthma patients who did not qualify to participate in the study were recruited to assist in the training. The entire treatment process for both treatment groups was demonstrated while the RAs observed. This included use of education and treatment scripts, development of imagery, and clinically appropriate delivery of induction and treatments. The entire in-service, including demonstrations, was videotaped with the permission of the volunteers. This videotape was available to the RAs for review.

For approximately 3 months, the new RA's administered treatments under the supervision of the SRA. I was available for phone consults, provided ongoing supervision, and conducted file reviews to ensure adherence to treatment protocols.

Treatment

The treatment protocol for this study was developed and tested in Zukiwski (1996). The treatment is based on descriptions of clinical work (Achterberg et al., 1994;

Norris, 1989; Rossman, 1984; Siegel, 1986; Simonton et al., 1978), research (e.g., Hall et al., 1992; Hall, Minnes, & Olness, 1993; Hall et al., 1996; Rider & Achterberg, 1989), and published protocols (Hall, 1990). Key elements of the current treatment protocol are discussed below with note of modifications of the 1996 protocol.

Written treatment protocols were used to standardize the delivery of both treatments. The protocols for each group were made as similar as possible with the exception of type of imagery. For example, the practice of the asthma specific imagery treatment features a series of instructions to imagine 6 separate images, each followed by a period where there are no instructions so the participant can practice the imagery in silence without distraction. Although the calm scene imagery practiced by the referent group consists of only 3 separate calm scene images, the pattern of 6 instructions followed by silence is maintained by providing 2 sets of verbal instructions for each calm scene image. Timing and pacing of the audio taped version of the script is identical for both treatments. I decided to use only 3 calm scene images because many people have difficulty creating more than 2 or 3 meaningful calm scene images.

Individual training sessions of 1 to 1.5 hours in length were conducted by the researcher or research assistants at the Faculty of Education Clinical Services, University of Alberta. With the exception of the initial treatment session, scheduled for 1.5 hours, sessions were 1 hour in length.

Treatment began with confirmation of informed consent and elaboration of case history to establish rapport. Possible secondary gains associated with asthma were explored by asking each participant if they were aware of any positive consequences of having asthma, and if any negative consequences might result if asthma decreased.

A modified version of Hall's (1990) pre-induction script prepared the participants for the induction and treatment process. The pre-induction is used to address misconceptions and/or fears that may be held about the treatment, and provide instructions on how to deal with intrusive thoughts. After a brief explanation of what "imagery" is, participants developed pre-treatment imagery to represent what asthma and their medications mean to them. Pre-treatment imagery was not incorporated into the treatment imagery in this study, but was instead used to facilitate rapport and increase

consistency with clinical practice. Homework instructions for drawing the imagery were provided (Appendix D). Drawing paper and colored pencils or felts were provided in the first session.

With the aid of a script (Appendix E) all participants were then given a verbal explanation of the pathophysiology of asthma, focusing on several key elements of the disease process: (a) the allergen-antibody complex which functions as an initial trigger for the release of mediators and proteins; (b) infiltration and recruitment of immune and inflammatory cells such as T-cells and eosinophils through a decrease in their activation and adhesive capacity; (c) infiltration of immune and inflammatory cells such as T-cells and eosinophils through a decrease in the activation of endothelial cells; (d) the release of eosinophil-derived cytotoxic proteins through a decrease in inflammatory cell activation; (e) constriction of the smooth muscles surrounding the bronchi; (f) and increased production of mucus. Although the initial presentation of the education material was standardized all participants were encouraged to ask questions if clarification was needed.

Based on clinical practice (e.g., Achterberg et al., 1994), general healing images (e.g., white ball of light) were incorporated as part of the treatment in Zukiwski (1996). General healing imagery was eliminated from the current protocol to control for type of image treatment.

The remaining time in session 1 was dedicated to developing imagery. The treatment group developed asthma specific imagery representing desirable cellular and functional changes (Appendix F). For example, decreased activation and adhesion of circulating neutrophils. Typically only the first 2 out of 6 images were developed in the first session. Participants generated their own images, but feedback and correction was provided as needed to ensure that the imagery was consistent with the desired immunological changes. The referent group developed calm scene imagery based on their personal experience. Clinical feedback was provided to make the calm scene imagery more effective. All participants were encouraged to make the imagery vivid and powerful. Both groups were instructed to draw the images developed in the session as homework, and to bring the drawings to the next treatment session.

A 20 minute audio taped script of the induction and respective imagery treatments (Appendix F and G) was provided for home practice. Participants were encouraged to practice once per day with the audiotape. Home practice was documented on the asthma diary.

Subsequent treatment sessions began with a review of diary data and new drawings, as well as debriefing of experiences during home practice. A modified version of Hall's (1990) induction, featuring progressive relaxation and hypnotic deepening techniques, was used to facilitate a state of relaxation and focused attention immediately prior to instructions to imagine the desired imagery. Induction and imagery treatment was standardized with a printed script for both treatment conditions (Appendix F and G). During the imagery practice, both groups were provided a brief period (1 minute) during which they could combine or integrate their separate images in any way they chose. If the individual did not wish to integrate the imagery, they were instructed to practice the image that they believed would be most beneficial.

Researchers read the script with clinically appropriate tone, rhythm, and pacing. Timing is provided on the script to ensure that the induction would be approximately 7 minutes long with a 13 minute period of imagery following. The intervention was practiced in a quiet environment, with the participant seated in a comfortable chair. Time was allowed following the treatment for appropriate debriefing. Participants were asked to draw as homework any new imagery that may have developed during the treatment session. A total of 8 treatment sessions were provided. Approximately 3 to 7 days after the final treatment session, post-treatment spirometry was performed. Participants were reminded to withhold medications for the same duration as prior to pre-treatment spirometry. Participants were not provided any instructions to practice relaxation or imagery immediately prior to, or even the same day of, the post-treatment spirometry. Completed asthma diaries were collected at this time.

Participants were debriefed immediately or soon after post-treatment spirometry. They were provided a brief description of changes in their lung function that occurred over the 8-week period. They were reminded that they will receive a summary

description of results from the study and will have an opportunity to learn about the imagery treatment they did not receive if it proved to be more effective.

CHAPTER 4: RESULTS

This was a two-way repeated measures design with repeated measures on one factor. The design allowed us to test 3 different effects: treatment effect alone, time effect alone, and the interaction between treatment and time (treatment * time). However, I was only clinically interested in testing the treatment * time interaction effects. The repeated measures analysis included the variables of age, gender, and severity as they may potentially be related to the response. However, for the purposes of this study, these variables were not of intrinsic interest in themselves.

Repeated measurements data occur when the same characteristic is measured on more than one occasion on the same observational unit. This type of data require special analyses as the error terms corresponding to the respective observational units are often correlated, and this additional structure must be accounted for in the analysis (Milliken & Johnson, 1992). Many techniques exist for the analysis of these data that can be broadly classified as either univariate or multivariate approaches (Crowder & Hand, 1990). A common univariate approach is the analysis of repeated measures model (often referred to as repeated measures ANOVA) for which each response at each occasion is modelled as a function of factors and/or covariates. In contrast, the multivariate approach models the vector of responses for each subject as a function of factors and/or covariates. While MANOVA requires a complete data vector for each subject, the repeated measures model can handle missing observations without resorting to imputation (Verbeke & Molenberghs, 2000). In this study the univariate approach was adopted for the following reasons. First, there was no a priori reason to expect complete data vectors for all subjects that would preclude the use of MANOVA (unless imputation was also used) for analyzing repeated measures data. Secondly, because sphericity is trivially satisfied when only two measurement occasions exist (i.e., for the primary hypotheses), the repeated measures approach may be more powerful than MANOVA (Crowder & Hand, 1990) and so is a reasonable alternative. Note that alternatively, one could also have simply worked with the differences in response (time 1-time 0 for instance) and used a regular one-way ANOVA to assess treatment (group) differences. However, because it was of interest to

assess the interaction effect between treatment and time, a two-way treatment structure is required.

Demographics and Effectiveness of Randomization

The 26 participants were randomly assigned to treatment and referent groups. Each group had 13 participants with 7 females and 6 males in the treatment group (Group A), and 11 females and 2 males in the referent group (Group B).

Eleven participants were withdrawn from the study. Five elected to withdraw before completing the study (2 from Group A; 3 from Group B). Three were withdrawn due to noncompliance with treatment and collection of diary data (2 from Group A; 1 from Group B). After the exclusion of these participants, each group had 9 subjects with the potential of completing the study. Unfortunately, three participants in Group B were withdrawn due to respiratory infections requiring a change in dosage of oral corticosteroids or administration of antibiotics. One of these individuals was hospitalized with pneumonia. Fifteen participants completed the study and were included in this analysis. Group A was composed of 5 females and 4 males; Group B had 5 females and 1 male.

To validate the effectiveness of randomization the balance in key potential confounding variables (gender, age, severity) in each group before and after attrition were investigated to see if balance was maintained between the groups. As shown in Table 1, the balance on these key variables was maintained in the two treatment arms. Although there were more women in the referent group at initial randomization and after attrition, the difference was not statistically significant. I am not aware of any gender effects that might influence outcomes with the treatments in this study. The mean age of participants in both groups was 46 years at randomization. After attrition the mean age of the treatment group at 54.7 years was slightly higher and the mean age of the referent group was unchanged. The difference in age was not statistically significant before ($p = 0.99$) or after ($p = 0.53$) attrition. Severity of asthma was expressed as a percentage of the predicted FEV_1 based on each individual's gender, age, and height. The treatment group was on average slightly more severe than the referent group, although the difference

Table 1
Comparison of groups before and after participant attrition.

Variable	Group		Test Result
	Treatment	Referent	
Before Attrition			
Gender (men/women)	6/7	2/11	$p = .09^a$
Age	$M = 46$ (25-64)	$M = 46.1$ (19-62)	$p = .99^b$
Severity[c]	$M = 54.7$ (34-78)	$M = 63.6$ (40-79)	$p = .13^b$
After Attrition			
Gender (men/women)	4/5	1/5	$p = .26^a$
Age	$M = 50.7$ (24-64)	$M = 45.5$ (24-62)	$p = .53^b$
Severity	$M = 52.6$ (34-78)	$M = 59.7$ (49-79)	$p = .37^b$

Note: Values for age and severity are means and range in parentheses.
[a] χ^2.
[b] Independent samples t-test.
[c] Severity of asthma is expressed as a percentage of the individuals predicted FEV_1.

did not approach statistical significance. Clinically, the difference was small, although the treatment group might have been expected to have more symptoms and increased likelihood of asthma exacerbation and respiratory infection. As mean severity of both groups was in the range of moderate to severe asthma, both groups would have been expected to have room for improvement in terms of lung function.

Volunteers were not tested for atopy but were asked to report any allergies. All but two participants who completed the study reported airborne allergies (Table 2). Participants 1 and 15 in the treatment group were not aware of any allergies. Participant 15 reported that past allergy testing was negative. Participant 14 in the treatment group reported allergy related asthma exacerbations but claimed to have occupational asthma related to long-term exposure to ammonia and other chemicals in industrial plants. The one subject in the previous study (Zukiwski, 1996) with severe occupationally related asthma had significant improvements in lung function during the study.

Provision of Treatment

As described in the methodology section, research assistants administered treatments during a portion of the study. Table 3 shows how many participants were treated by each experimenter and how many of those participants were withdrawn or completed the study. The researcher (Therapist A) provided treatment for 17 out of the original 26 participants (65%) and 9 out of the 15 who completed the study (60%). The number of participants that each research assistant provided treatment to was relatively balanced. Each research assistant provided treatment to participants that completed the study. In the discussion of clinical improvement later in the results section, Tables 8 and 9 illustrate that each therapist had at least one participant who had a clinically significant improvement in lung function. Using more than one therapist to administer the treatments provides support to the notion that treatment effects are related to the treatment itself and not primarily the characteristics of one therapist. As well, this helps to illustrate that the other therapists can learn to deliver the treatment effectively.

Table 2
Severity, airborne asthma, and occupational asthma.

Group	Subject	Severity [a]	Airborne Allergies [b]	Occupational Asthma [c]
Treatment	1	Moderate	-	-
	2	Moderate	+	-
	6	Severe	+	-
	8	Severe	+	-
	9[c]	Moderate	+	-
	11	Moderate	+	-
	13	Severe	+	-
	14	Severe	+	+
	15	Severe	-	-
Referent	3	Severe	+	-
	4	Moderate	+	-
	5	Severe	+	-
	7	Moderate	+	-
	10	Severe	+	-
	12	Severe	+	-

Note.
[a] Asthma severity based on degree of airflow obstruction (FEV_1% of predicted). Mild = >80%, Moderate = 60-80%, Severe = <60% (Boulet et al., 1999).
[b] Self-reported history of airborne allergies indicating atopy.
[c] Onset of asthma reportedly due to occupation related exposure to toxins or irritants.

Table 3
Provision of treatment by therapists: Breakdown by group and therapist.

		Therapist[a]				
	Group	A	B	C	D	Total
Breakdown by group	Treatment	5	1	2	1	9
	Referent	4	1	1	0	6
Total that completed study		9	2	3	1	15
Total Withdrawn		8	0	1	2	11

Note:
[a] Therapist A is the researcher, therapists B is the senior research assistant, therapists C and D are research assistants.

Description of Primary Analysis

The primary statistical objective, for which the study was designed, was to build a statistical model so that the effect of intervention (coded as the "group" factor), time and most importantly the group and time interaction on the various continuous responses (FEV_1, FVC, PEF) could be assessed. To analyze the repeated measures data, a univariate linear model was fitted to the data. The model included as predictors a constant (intercept) term, intervention, time, and the interaction between intervention and time. Also included in the model were predictors thought to be confounders: age, severity and gender.

Exploratory Data Analysis (EDA). First I explored the distribution of the response variable for each of the treatment arms. In addition, this allows for a preliminary assessment of outlying observations and whether or not to expect significant treatment effects in a confirmatory analysis. Scatter plots were then produced between each of the continuous responses and continuous predictors (time, age and severity) to assess whether or not these variables should enter the model linearly, or nonlinearly (e.g., quadratic or higher order polynomial). Note that because time was measured at only two occasions it entered linearly as no higher order polynomial can be deduced from only two points. The variables age and severity appeared to have nonlinear quadratic effects on the responses, however due to the small sample size it was felt that a simpler linear effect would suffice. In summary, time, age and severity entered statistical models as linear effects.

Model Fitting. A univariate linear model was fitted to the data using the repeated measures procedure in SPSS 10. This model accommodates multiple measures on the same subject where these measurements may be correlated. All predictors entered the model simultaneously to ensure that each variable's effect was adjusted for the potential confounding effects of age, gender and severity.

Model Assessment (Goodness of Fit Assessment). Following the fitting of each model to the data, residual analysis was performed to ensure that the model residuals adhered to the required assumptions (normality and constant variance). Normal probability plots were used to assess normality and a plot of the standardized residuals

against their predicted values were used to assess constant variance and any indication of outlying observations. No remedial measures were necessary as the models reasonably satisfied these assumptions.

Primary Efficacy Variables

The primary efficacy variables were FEV_1, FVC, and PEF obtained by pre- and post-treatment spirometry. It is not recommended to evaluate changes in FEF_{25-75} in clinical trials as improvements in FVC or FEV_1 may produce paradoxical decreases in FEF_{25-75} (Enright et al, 1994). Despite the limitations of FEF_{25-75} in between-group comparisons, it may be valuable to determine if any changes in this measure were consistent with changes in primary efficacy measures. In light of the limitations, FEF_{25-75} data is presented in the section on secondary efficacy variables.

As spirometry was performed before and after administration of bronchodilator medication, I have two sets of spirometric data to evaluate changes over time (pre- vs. post-treatment changes). Pre-bronchodilator data represents the degree of airway obstruction due to airway inflammation (e.g., narrowing of airways due to edema) combined with bronchoconstriction. Bronchoconstriction is influenced by multiple factors, only a few of which include: environmental exposures (e.g., cold air), time of last medication, stress, and exercise. Post-bronchodilator data represents degree of airway obstruction due to airway inflammation (with bronchoconstriction removed). Pre- and post-treatment comparison of post-bronchodilator FEV_1 is the most useful measure in clinical trials and represents the best lung function that can be achieved by bronchodilator therapy (Enright et al., 1994). Patients with hyperresponsive airways and persistent bronchoconstriction may show no or only minor changes in pre-bronchodilator lung function despite significantly decreased airways inflammation. Only when the bronchoconstriction is removed with bronchodilator medication can the clinical improvement resulting from decreased inflammation be seen.

Degree of bronchodilator induced reversibility was not evaluated. While it is valuable to interpret clinically on a case-by-case basis, it is not useful as an outcome measure in clinical trials (Enright et al., 1994).

With this repeated measures design, the primary goal was to assess treatment and time interaction effect. The effect of treatment on the response was dependent on time. Conversely, the effect of time on the response in question depended on which treatment arm the participants were in. Only one of the interaction plots (post-bronchodilator PEF) reached statistical significance at the 5% level of significance. I calculated that the power for the other interactions was very low (less than 30% in each case). Although FEV_1 is the primary measure for assessing change in airways obstruction (Blaiss, 1997) and FVC may be the most relevant indicator of reversal of peripheral airway pathology (Bailey, Wilson, Weiss, Windsor, & Wolle, 1994), I will present PEF first because the change on this measure was statistically significant. PEF and FEV_1 are not equally sensitive to bronchospasm or airway narrowing that does not occur equally in the lung (Enright et al., 1994). PEF measures flow at high lung volume and FEV_1measures flow at high and mid volumes. While some of these interaction effects were statistically insignificant, this was a pilot study and the nature of the effect was important to investigate. Interaction plots are used to illustrate the treatment * time interactions. The results of data obtained by spirometry are summarized in Table 4.

Pre- and Post-Bronchodilator PEF Obtained by Spirometry

Pre-bronchodilator PEF. The repeated measures analysis resulted in an interaction effect between treatment and time on pre-bronchodilator PEF that was not statistically significant ($F = 1.13$, $p = 0.31$). The interaction effect between treatment and time for pre-bronchodilator PEF did not markedly change when controlling for age, gender, or severity.

The interaction plot for pre-bronchodilator PEF (Figure 2) illustrates the relative changes between the treatment and referent groups. As seen in Figure 2, the effect of treatment depends on which time point you are at. While the mean PEF for the treatment group increased 7.7% from 6.61 litres per second (L/s) before treatment at Time 0 (T0) to 7.12 L/s after treatment at Time 1 (T1), the mean PEF for the referent group was unchanged (0.1% increase) from 6.64 to 6.65 L/s.

Table 4
Results from spirometry.

	Group				Test Result	
	Treatment		Referent			
Outcome Measures	Time 0	Time 1	Time 0	Time 1	F	p
PEF Pre-β_2	6.61 (.8059)	7.12 (.8950)	6.64 (.6193)	6.65 (.8581)	1.13	0.31
PEF Post-β_2	7.12 (.8224)	7.72 (.9104)	7.57 (.6798)	7.43 (.763)	4.02	0.036*
FEV_1 Pre-β_2	1.7 (.1759)	1.82 (.2095)	1.81 (.1888)	1.82 (.2219)	1.15	0.30
FEV_1 Post-β_2	1.97 (.1998)	2.1 (.2412)	2.08 (.1615)	2.07 (.1322)	2.10	0.17
FVC Pre-β_2	2.85 (.3422)	3.04 (.4237)	2.79 (.1425)	2.98 (.2095)	0.42	0.53
FVC Post-β_2	3.13 (.3495)	3.33 (.4352)	3.16 (.1852)	3.21 (.1692)	0.85	0.37

Note: Mean values of spirometric measures before and after beta-agonist (β_2) bronchodilator before (Time 0) and after (Time 1) treatment with standard error in parentheses. FVC = forced vital capacity. FEV_1 = forced expiratory volume in 1 s. PEF = peak expiratory flow. PEF is in Litres per second, FEV_1 and FVC are in Litres. F statistic and p values from repeated measures analysis. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.
*Statistically significant

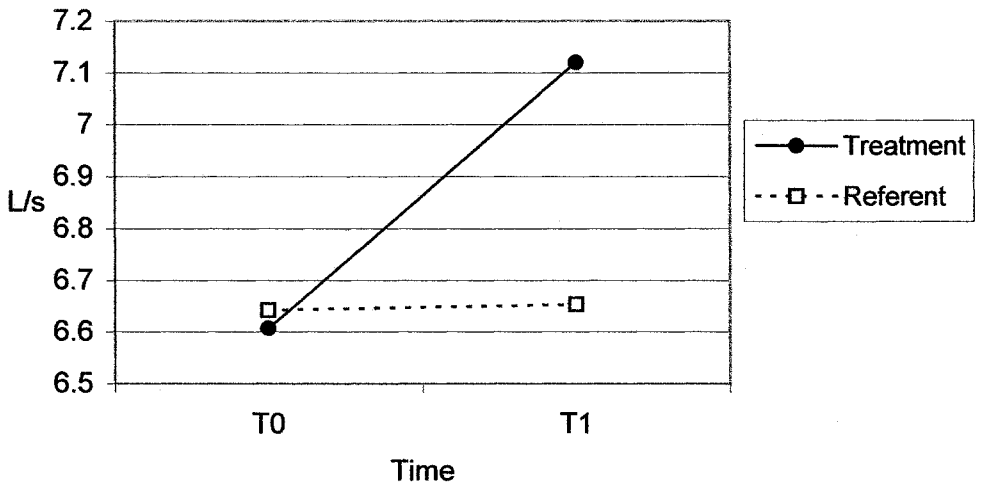

Figure 2. Pre-bronchodilator PEF interaction between treatment and time. Displays the mean pre-bronchodilator peak flow in litres per second (L/s) obtained by spirometry for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). Treatment * time interaction was not statistically significant ($F = 1.13$, $p = 0.31$). Treatment group mean PEF was 6.61 at T0 and 7.12 at T1, increasing 7.7%. Referent group mean PEF was unchanged (6.64 at T0 and 6.65 at T1). The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

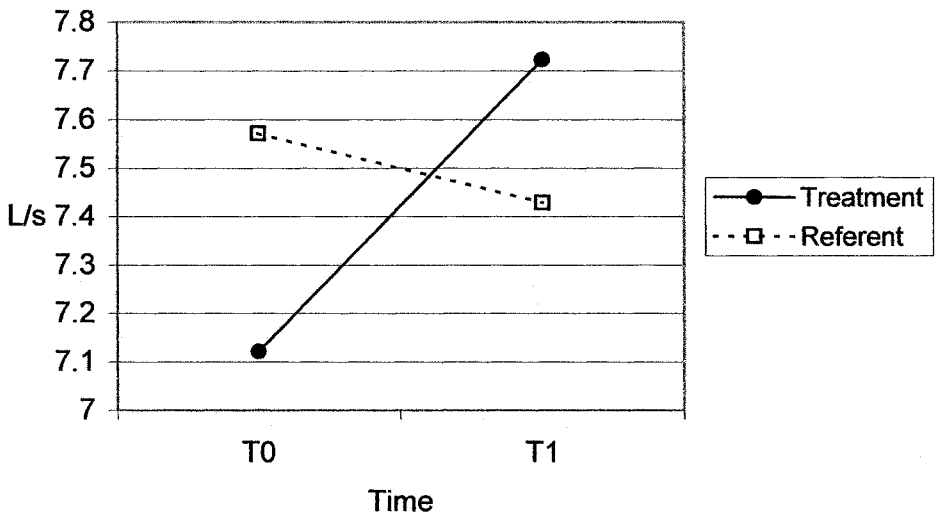

Figure 3. Post-bronchodilator PEF interaction between treatment and time. Displays the mean post-bronchodilator peak flow in litres per second (L/s) obtained by spirometry for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). Treatment * time interaction was statistically significant ($F = 4.02$, $p = 0.04$). Treatment mean PEF was 7.12 at T0 and 7.72 at T1, increasing 8.4%. Referent mean PEF was 7.57 at T0 and 7.43 at T1, decreasing 1.8%. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

Post-bronchodilator PEF. The repeated measures analysis, with age included as a covariate, resulted in a significant interaction effect between treatment and time on post-bronchodilator PEF with an F of 4.02 and a p value of 0.04 (Figure 3). The mean PEF for the treatment group increased 8.4% from 7.12 to 7.72 L/s and the mean PEF for the referent group decreased 1.8% from 7.57 to 7.43 L/s. Mean PEF for the treatment group was lower than the referent group before treatment. This was consistent with the demographic data which showed that overall the treatment group had slightly more severe asthma. After 8 weeks of practicing immune specific imagery, the treatment group improved in post-bronchodilator PEF to a level above the mean PEF for the referent group before treatment or after treatment. The referent group had a slight decrease in mean PEF after 8 weeks of practicing relaxation imagery. After adjusting for the multiple analyses conducted during the data analysis, this one significant finding was no longer statistically significant.

Pre- and Post-Bronchodilator FEV_1

The repeated measure analysis resulted in an insignificant interaction effect between treatment and time on pre-bronchodilator FEV_1 ($F = 1.15$, $p = 0.30$) and post-bronchodilator FEV_1 ($F = 2.10$, $p = 0.17$). I appreciate that these are not statistically significant but showing the interaction is clinically significant because PEF, FEV_1 and FVC are different but related aspects of lung function. If the interaction plots show similar patterns for FEV_1 and FVC, this would support the notion that the results seen with PEF are consistent with improved lung function.

Pre-bronchodilator FEV_1. As shown in Figure 4, the mean FEV_1 for the treatment group was lower than the referent group prior to treatment. This was consistent with the demographic data which revealed that the treatment group overall had slightly more severe asthma (although the difference was not statistically significant). The mean pre-bronchodilator FEV_1 for the treatment group increased 7.1% from 1.7 litres (L) at T0 to 1.82 L at T1 showing an overall improvement in lung function. The mean FEV_1 for the referent group was relatively unchanged (0.5%) from 1.81 to 1.82 L. The interaction

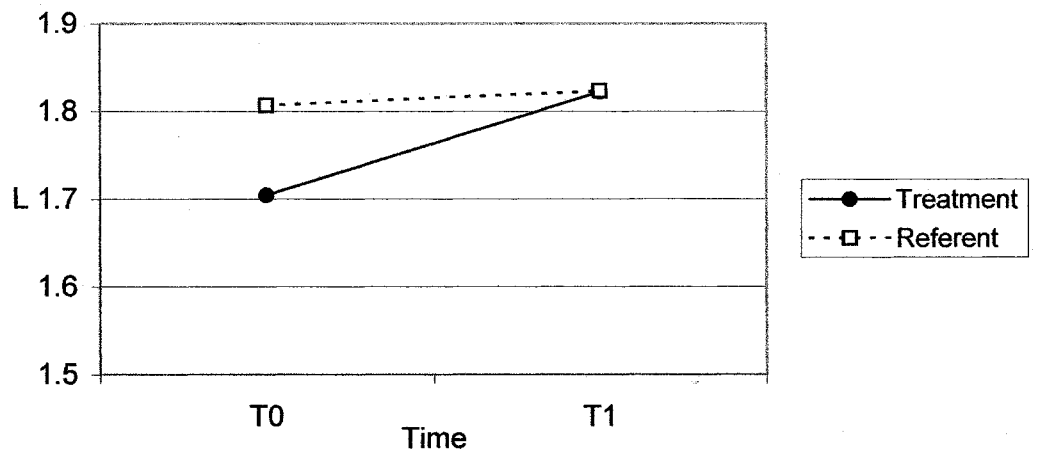

Figure 4. Pre-bronchodilator FEV_1 interaction between treatment and time. Displays the mean pre-bronchodilator FEV_1 in litres (L) for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). Treatment * time interaction was not statistically significant ($F = 1.15$, $p = 0.30$). Treatment group mean FEV_1 was 1.7 at T0 and increased 7.1% to 1.82 at T1. Referent group mean FEV_1 was 1.81 at T0 and 1.82 at T1, increasing 0.5%. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

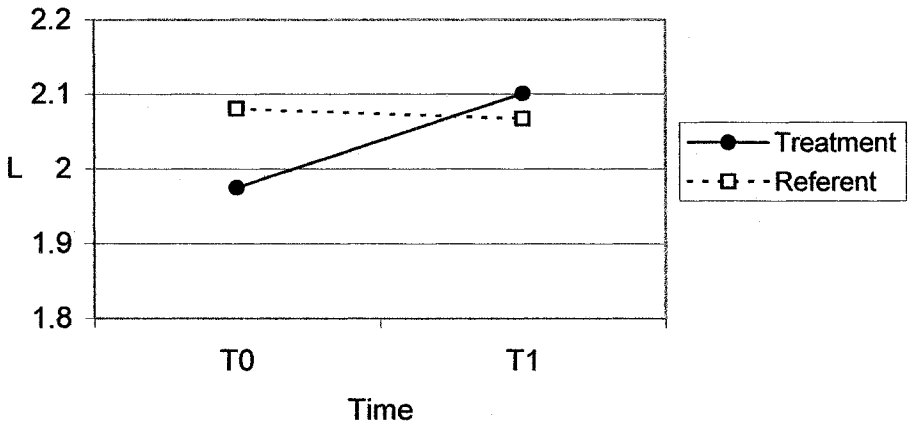

Figure 5. Post-bronchodilator FEV_1 interaction between treatment and time. Displays the mean post-bronchodilator FEV_1 in litres (L) for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). Treatment * time interaction was not statistically significant ($F = 2.10$, $p = 0.17$). Treatment group mean post-bronchodilator FEV_1 was 1.97 at T0 and 2.1 at T1, increasing 6.6%. Referent group mean FEV_1 was 2.08 at T0 and decreased 0.5% to 2.07 at T1. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

plot shows that the treatment group's mean FEV_1 increased to the same level as the referent group at T1.

Post-bronchodilator FEV_1. Similar to changes in pre-bronchodilator FEV_1, the mean post-bronchodilator FEV_1 for the treatment group increased 6.6% from 1.97L at T0 to 2.1L at T1, and the referent group was relatively unchanged (-0.5%) from 2.08 to 2.07L (Figure 5).

Pre- and Post-Bronchodilator FVC

Pre-bronchodilator FVC. The interaction effect between treatment and time was insignificant on pre-bronchodilator FVC ($F = 0.42$, $p = 0.53$). As shown in Figure 6, pre-bronchodilator FVC for the treatment group increased 6.7% from 2.85L at T0 to 3.04 L at T1, and the referent group increased 3.6% from 2.79L at T0 to 2.98L at T1.

Post-bronchodilator FVC. The interaction effect between treatment and time was insignificant on post-bronchodilator FVC ($F = 0.85$, $p = 0.37$). Similar to changes in pre-bronchodilator FVC, post-bronchodilator FVC for the treatment group increased 6.4% from 3.13L at T0 to 3.33L at T1, and the referent group increased 1.6% from 3.16L to 3.21L (Figure 7).

Summary of Primary Efficacy Data Results

Airway narrowing due to inflammation and bronchoconstriction causes increased resistance to airflow. As FEV_1 and PEF are both affected by resistance to airflow they serve as measures of airway obstruction. FEV_1 is the best measure of airway obstruction. While PEF has more variability and is more influenced by effort it is still a useful measure of lung function.

On pre- and post-bronchodilator FEV_1 and PEF obtained by spirometry the treatment group improved between approximately 7 to 8 percent while the referent group was unchanged or showed a slight decrease (changes from 0 to -2%). Repeated measures analysis resulted in a statistically significant treatment * time interaction effect for post-bronchodilator PEF. In other words, after 8 weeks of treatment using immune system imagery the treatment group showed greater improvement in lung function than the referent group which practiced relaxation imagery.

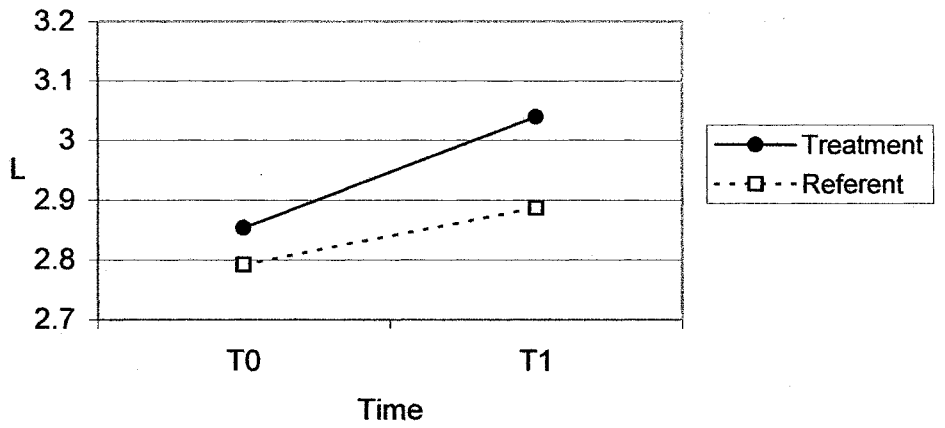

Figure 6. Pre-bronchodilator FVC interaction between treatment and time. Displays the mean pre-bronchodilator FVC in litres (L) for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). Treatment * time interaction was not statistically significant ($F = 0.42$, $p = 0.53$). Treatment group mean FVC was 2.85 at T0 and 3.04 at T1, increasing 6.7%. Referent group mean FVC was 2.79 at T0 and 2.98 at T1, increasing 3.6%. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

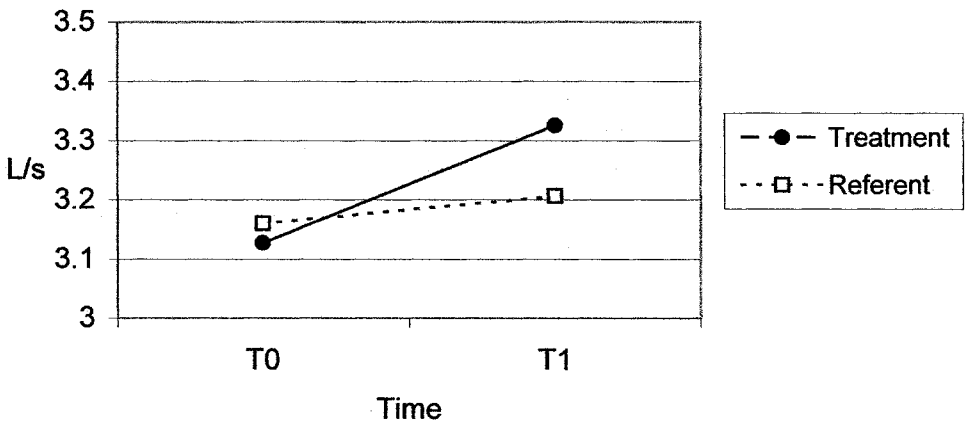

Figure 7. Post-bronchodilator FVC interaction between treatment and time. Displays the mean post-bronchodilator FVC in (L) for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). The treatment * time interaction was not statistically significant ($F = 0.85$, $p = 0.37$). Treatment group mean FVC was 3.13 at T0 and 3.33 at T1, increasing 6.4%. Referent group mean FVC was 3.16 at T0 and 3.21 at T1, increasing 1.6%. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

FVC represents the total volume of air expired in a forced expiratory maneuver. Increases in FVC represent increases in airway caliber due to decreased airway inflammation and decreased air trapping. Both the treatment and referent groups showed increases in pre- and post-bronchodilator FVC. The treatment group improved approximately 6.5% in both pre- and post-bronchodilator FVC. The referent group increased 3.6% on pre-bronchodilator FVC and 1.6% on post-bronchodilator FVC. Although the difference between the groups was not statistically significant, the increased FVC in the treatment group was consistent with the improvements in FEV_1 and PEF. There was a small overall improvement in the referent group FVC.

Changes in pre-bronchodilator measures indicated decreases in bronchoconstriction and/or airway inflammation. Bronchoconstriction can be influenced by variables such as stress, exertion, and environmental conditions (e.g., cold air) that change on a short-term basis. Measurements obtained in post-bronchodilator spirometry represent the best lung function that can be obtained with bronchodilator therapy. Changes in post-bronchodilator measures lung function are more indicative of changes in airway inflammation. Finding a statistically significant improvement in a post-bronchodilator measure of lung function supports the hypothesis that the improved lung function in the treatment group is due to decreased inflammation and not just decreased bronchoconstriction.

Although they did not reach statistical significance, the interaction between treatment and time on FEV_1 and FVC are consistent with those seen for PEF. These findings are also consistent with improvements in lung function seen in Zukiwski (1996).

Power Analysis. A power analysis was conducted using the data from this study to estimate the sample size required for adequate power. For a power of 80% with an effect size of 15% increase over baseline, 15 per group would be needed for pre-bronchodilator FEV_1 and post-bronchodilator PEF, and 12 per group for post-bronchodilator FEV_1.

Secondary Efficacy Variables

This study was designed to use pre- and post-treatment spirometry as the primary outcome measures. Daily diary data that included PEF measured on a Mini-Wright Peak Flow Meter (MPFM) and self-reports of symptoms and medication usage were also collected as supplementary data. FEF_{25-75} obtained by spirometry will also be presented within this section.

Pre- and Post-Bronchodilator FEF_{25-75}

It is recommended that FEF_{25-75} should not be used for trend analysis in clinical trials since paradoxical changes may occur (Enright et al., 1994). For example, in this study participant #8 had an 18% increase in FVC and an 11% increase in post-bronchodilator FEV_1. This is a clinically relevant improvement on both measures. However, FEF_{25-75} paradoxically decreased 13% creating the false impression that this participant's lung function deteriorated if FEF_{25-75} was viewed in isolation.

However, in many cases improvement in lung function as indicated by an increase in FEV_1 will also be reflected by an increase in FEF_{25-75}. As well, some patients may have clinically relevant improvements in FEF_{25-75} with no or little improvement in FVC or FEV_1. For example, in this study, participant #2 had no change in pre-bronchodilator FVC and only a 6% increase in FEV_1 yet there was a 24% increase in FEF_{25-75}. Despite the limitations of FEF_{25-75} as an outcome measure, I felt it would be worthwhile to examine the treatment * time interaction. Repeated measures analysis was performed on the complete data set without removing subjects with paradoxical changes in FEF_{25-75}. As part of the exploratory analysis, I removed those participants from the data set who had changes in their FEF_{25-75} that was paradoxical to changes in FVC and FEV_1. Repeated measures analysis was then performed on the new data set, the results and interaction plots are presented below for comparison with the complete data set.

Pre-bronchodilator FEF_{25-75}. The interaction effect between treatment and time for pre-bronchodilator FEF_{25-75} was not statistically significant ($F = 0.80$, $p = 0.39$). As shown in Figure 8, the mean FEF_{25-75} for the treatment group increased 6.1% from 0.98 L/s to 1.04 L/s while the referent group decreased 3.3% from 1.21 L/s to 1.17 L/s. This

suggests that overall there was an improvement in the small airway in the treatment group and an overall slight decline for the referent group.

Post-bronchodilator FEF_{25-75}. The interaction effect on post-bronchodilator FEF_{25-75} was also not statistically significant ($F = 2.40$, $p = 0.15$). As shown in Figure 9, the mean post-bronchodilator FEF_{25-75} for the treatment group increased 9.8% from 1.22 L/s to 1.34 L/s and the referent group decreased 6.1% from 1.31 L/s to 1.23 L/s. Consistent with changes seen in other measures of lung function presented in the primary analysis, the post-bronchodilator improvement in FEF_{25-75} for the treatment group was greater than the improvement in pre-bronchodilator FEF_{25-75}. Although insignificant, the pattern of treatment * time interaction for FEF_{25-75} was consistent with those of pre- and post-bronchodilator PEF, FEV_1, and FVC. On all outcome measures obtained by spirometry, the treatment group had greater improvements in lung function (between approximately 6 and 10%) than the referent group which varied between increasing approximately 3% and decreasing 6%.

FEF_{25-75} with paradoxical responders removed. As explained earlier, decreased FEF_{25-75} may be seen in some cases despite clinically significant improvement in FEV_1 or FVC. The decrease in FEF_{25-75} does not accurately represent the improvement in lung function that occurred. I removed participants from the data set if they had decreased FEF_{25-75} and increases in both FVC and FEV_1 (see Table 5). After removing participants 8, 9, and 14 from the pre-bronchodilator FEF_{25-75} data set, the groups were balanced, each with 6 participants. The interaction effect appears to be stronger for pre-bronchodilator FEF_{25-75} with the paradoxical responders removed (Figure 10). However, the treatment * time interaction was not statistically significant ($F = 2.0$, $p = 0.188$) and power was low (25%). Mean FEF_{25-75} for the treatment group improved 13.5% from 0.96 to 1.09 L/s. Before removing the paradoxical responders, the treatment group mean increased only 6.1%. Including the paradoxical responders in the analysis had falsely suppressed the treatment group post-treatment mean. Even though 3 participants were removed from the treatment group, two of whom had clinically significant improvements in FVC or FEV_1, the overall improvement in FEF_{25-75} for the treatment group is still quite notable.

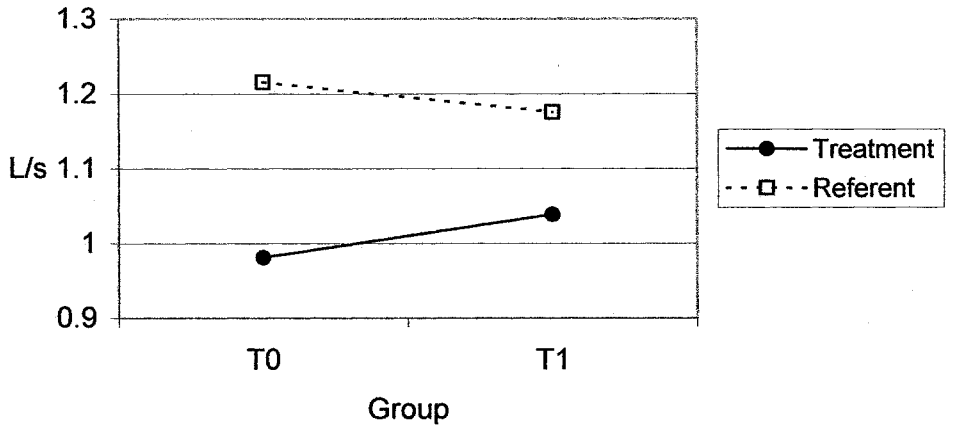

Figure 8. Pre-bronchodilator FEF_{25-75} interaction between treatment and time. Displays the mean FEF_{25-75} in litres per second (L/s) for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). Treatment * time interaction effect was not statistically significant ($F = 0.80$, $p = 0.39$). Treatment group mean FEF_{25-75} was 0.98 at T0 and increased 6.1% to 1.04 at T1. Referent group mean FEF_{25-75} was 1.21 at T0 and 1.17 at T1, decreasing 3.3%. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

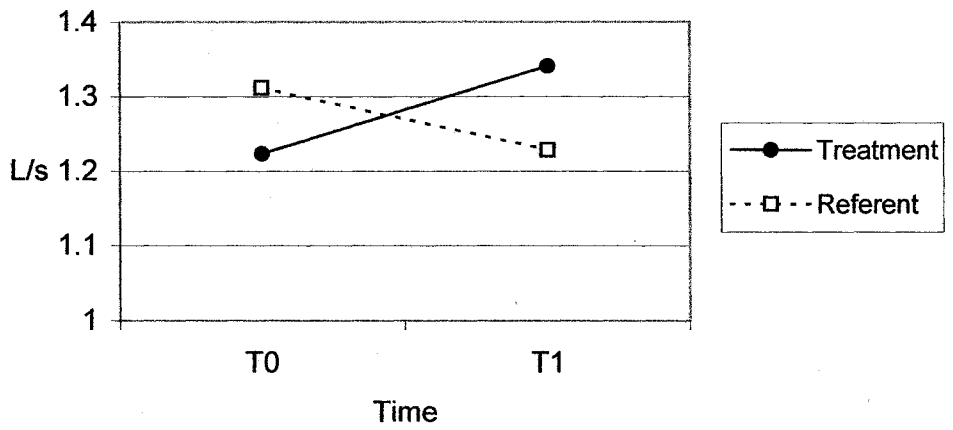

Figure 9. Post-bronchodilator FEF_{25-75} interaction between treatment and time. Displays the mean FEF_{25-75} in litres per second (L/s) for both the treatment and referent groups before treatment at Time 0 (T0) and after treatment at Time 1 (T1). Treatment * time interaction effect was not statistically significant ($F = 2.40$, $p = 0.15$). Treatment group mean FEF_{25-75} was 1.22 at T0 and increased 9.8% to 1.34 at T1. Referent group mean FEF_{25-75} was 1.31 at T0 and 1.23 at T1, decreasing 6.1%. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

Table 5

FEF_{25-75} paradoxical responders.

			Pre- to Post-Treatment Change (%)		
Data	Group	Subject	FVC	FEV_1	FEF_{25-75}
Pre-bronchodilator	Treatment	8	15.5*	5.8	-22.1
		9	7.5	3.4	-11.7
		14	10.4	25.6*	-1.5
Post-bronchodilator	Treatment	8	17.6*	11	-12.6
		13	17.7*	7	-12.1
	Referent	7	6.5	0.5	-13.64
		10	10.3	0.6	-3.7

Note. Table shows participants with paradoxical changes in FEF_{25-75} removed from the data set during exploratory analysis. They paradoxically had decreased FEF_{25-75} despite increases in both FVC and FEV_1. FVC = forced vital capacity. FEV_1 = forced expiratory volume in 1 s. FEF_{25-75} = mean forced expiratory flow between 25% and 75% of the expired vital capacity.
*Clinically significant improvement.

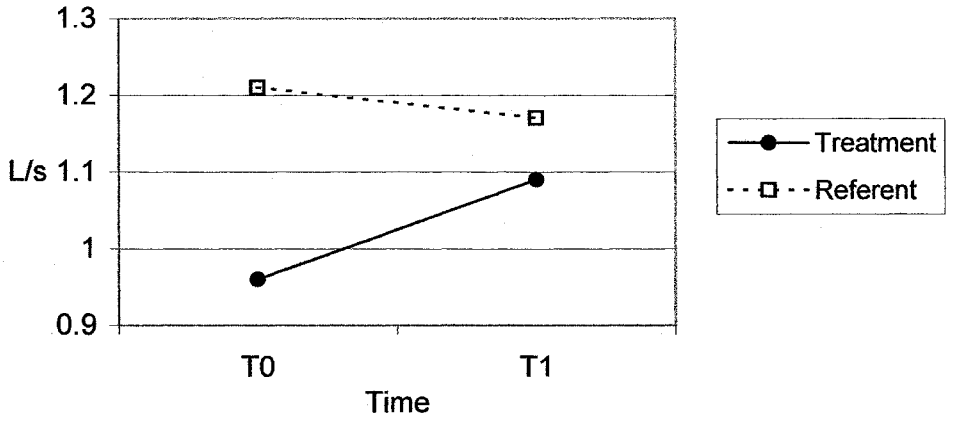

Figure 10. Pre-bronchodilator FEF_{25-75} with paradoxical responders removed. Treatment group mean FEF_{25-75} was 0.96 at T0 and 1.09 at T1, increasing 13.5%. Referent group mean FEF_{25-75} was 1.21 at T0 and 1.17 at T1, decreasing 3.3%. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

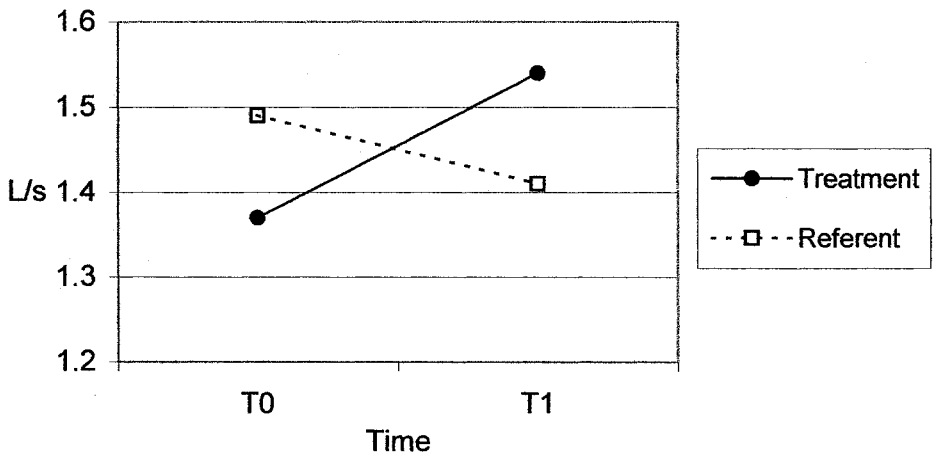

Figure 11. Post-bronchodilator FEF_{25-75} with paradoxical responders removed. Treatment group mean FEF_{25-75} was 1.37 at T0 and 1.54 at T1, increasing 12.4%. Referent group mean FEF_{25-75} was 1.49 at T0 and decreased 5.4% to 1.41 at T1. The treatment group practiced immune specific imagery and the referent group practiced relaxation imagery.

Participants 7, 8, 10, and 13 were removed from the post-bronchodilator FEF_{25-75} data set. Seven participants in the treatment group and 4 in the referent group remained. The treatment group mean FEF_{25-75} increased 12.4% from 1.37 to 1.54 L/s (Figure 11). Using the complete data set the treatment group mean increase was 9.8%. Removing the paradoxical responders altered the change in referent group mean FEF_{25-75} slightly. With paradoxical responders removed, the referent group mean decreased 5.4% from 1.49 to 1.41 L/s. The referent group mean had decreased 6.1% using the complete data set. The treatment * time interaction was not statistically significant ($F = 2.3$, $p = 0.167$) and power was low (27%). With low power in the pre- and post-bronchodilator analysis, no firm conclusions can be made.

Daily Peak Expiratory Flow

Daily self-report PEF can be useful in evaluating trends of change in lung function. PEF data presented in this section is different than PEF obtained by spirometry that was presented in the primary analysis. Daily PEF may be more influenced by patient effort because unlike during spirometric assessment, participants are not coached to provide their best effort. However, participants in the current study were trained in the proper use of a peak flow meter and instructed to exhale into the peak flow meter with maximum effort three times and record the highest reading. Daily PEF data has the advantage of multiple data points, where as spirometry was performed only twice during this study.

One of the most important differences between the two types of PEF measures is that patients were instructed to withhold short- and long-acting bronchodilators prior to spirometric assessment. Bronchodilating medications were not withheld prior to daily PEF measurement. Participants were instructed to record their PEF in the morning (AM PEF) and evening (PM PEF) prior to use of medication. As a result, AM PEF data should not be influenced by short-acting bronchodilator use unless participants used reliever medication in the early hours after waking with symptoms or if they were non-compliant and recorded PEF after administering medication. PM PEF may be influenced by use of short-acting bronchodilators during the day. Some participants rarely used short-acting bronchodilator medication, while others used them daily.

Patients treated with long-acting bronchodilators may have daily peak flow readings that do not accurately represent changes in the degree bronchoconstriction or airways inflammation. In this study, at least one type of long-acting bronchodilator was used by 5 participants in the treatment group and 2 participants in the referent group. Use of short- and long-acting bronchodilators will be discussed in greater detail later in the results section.

When visually interpreting plots of PEF data it is important to consider that PEF measurements can have a high degree of variability. Not only is asthma inherently variable as a disease, but bronchoconstriction is influenced by environmental factors such as air temperature, humidity, and airborne irritants. Even caffeine consumption can influence degree of bronchoconstriction. Changes in PEF are not expected to increase continuously throughout the study period. I do not know what degree of improvement in daily PEF is possible, especially in those taking long-acting bronchodilators. In a previous study (Zukiwski, 1996) overall improvement in AM and PM PEF were seen within the first 4 weeks. Some additional improvement was observed during the remainder of the 8-week treatment period. However, day-to-day changes in PEF were quite variable.

There are no clear guidelines for the presentation, analysis, and interpretation of daily PEF data. To determine how to approach the PEF data, literature on PEF was reviewed and the use of PEF in a number of clinical trials was examined. It was determined that comparing the weekly means of the two groups would be appropriate for a secondary analysis. Using weekly means facilitates clinically relevant evaluation of trends as percent change between two time points is easily calculated. The mean AM and PM peak flow for each week was calculated for each participant. This weekly mean was used in a repeated measures analysis.

While the weekly mean PEF provides an overall indication of how well each participant was doing during a given week, the highest PEFs achieved may be more clinically useful. Asthma patients are often instructed to determine their personal best PEF. This is the highest PEF attained when asthma is well controlled. This personal best is used as a baseline for comparing decreases in peak flow occurring during asthma

exacerbation. Several participants in this study as well as in Zukiwski (1996) excitedly reported they had achieved new personal bests during the study and saw this as evidence they were improving. I will present analysis of the weekly mean PEFs then examine weekly best PEFs.

Weekly mean PEF. Repeated measures analysis of AM PEF was not statistically significant ($F = 1.907$, $p = 0.099$). The power was moderately high at 64%. As seen in Figure 12, AM PEF for the referent group appears to be more variable than the treatment group. The treatment group appears to have had an overall gradual increase in AM PEF while the referent group had two periods of reduced PEF followed by a gradual increase with overall no improvement. Overall improvement of the treatment group was consistent with the analysis of FEV_1, PEF, FVC, and FEF_{25-75} obtained by spirometry.

Repeated measure analysis of PM PEF was also not statistically significant ($F = 0.863$, $p = 0.711$). Power was low at 27%. Figure 13 shows that the treatment group increased in week 2, decreased in week 3 and 4 and then slowly improved over the remaining weeks. The referent group slowly decreased over the first 7 weeks of the study then increased in week 8. Overall, there appears to be a slight trend in improvement for the treatment group that is consistent with the AM PEF data.

The weekly mean AM PEF for the treatment (Figure 14) and referent (Figure 15) groups was plotted to illustrate the individual trends. Line patterns were used to differentiate individual participants when lines overlapped. As the scale used in these figures is large, a relatively small change in PEF may be significant for that individual. For example, a change from 350 to 400 L/min is a 14% improvement. Interpretation of trends will be limited to visual analysis. Some participants had large and relatively steady changes and a trend is readily apparent. Smaller trends are more difficult to determine, especially with variable data.

Trends of increasing AM PEF are most apparent for participant 8 from the treatment group (Figure 14). Small trends in improvement occurred for participants 1 and 6 in the treatment group (Figure 14) and participant 4 in the referent group (Figure 15).

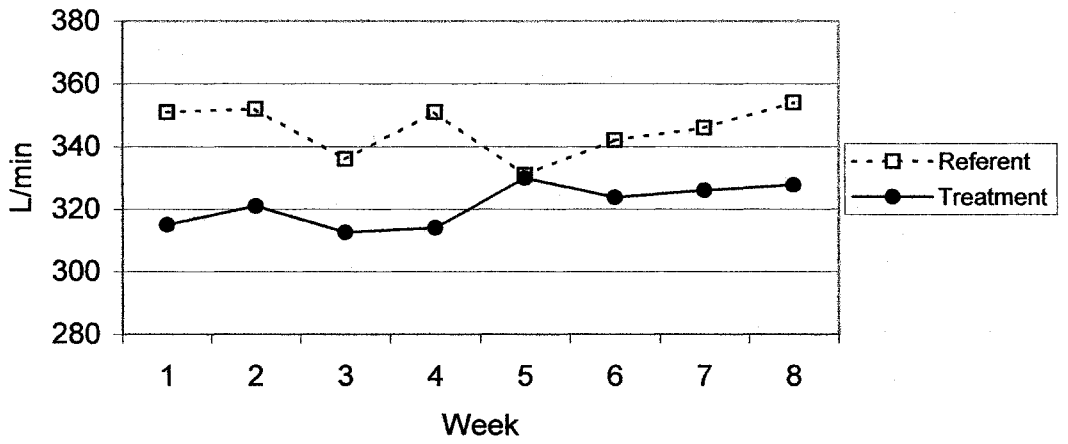

Figure 12. Weekly mean AM PEF. Weekly means for AM PEF recorded daily on an asthma diary were calculated for each participant. These means were used to calculate the group means for each week of the study. Repeated measures analysis was not statistically significant ((F = 1.907, p = 0.099).

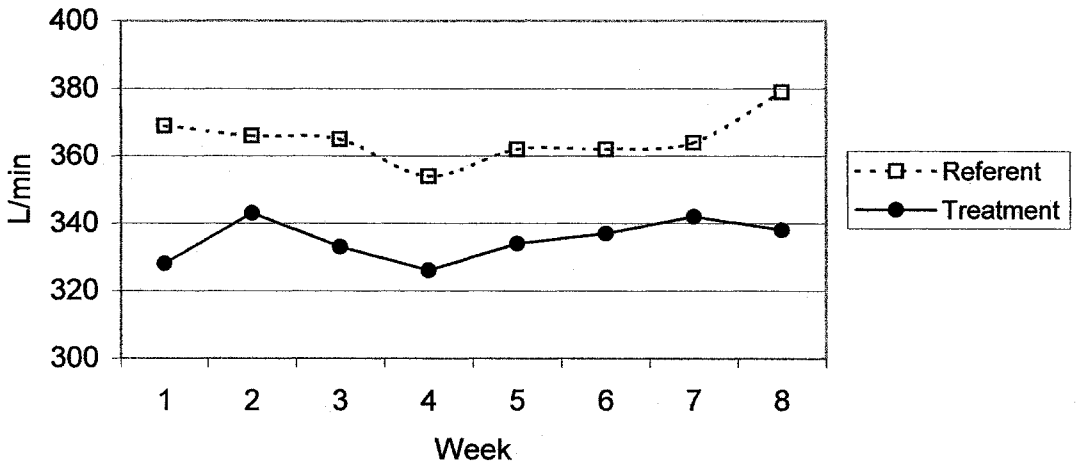

Figure 13. Weekly mean PM PEF. Weekly means for PM PEF recorded daily on an asthma diary were calculated for each participant. These means were used to calculate the group means for each week of the study. Repeated measures analysis was not statistically significant (F = 0.873, p = 0.711).

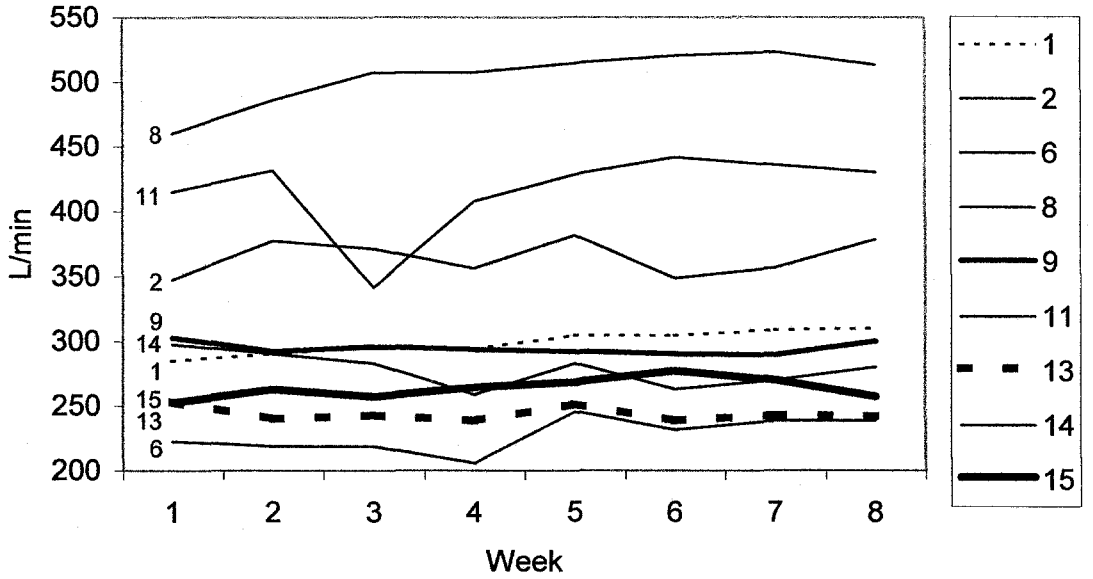

Figure 14. Treatment group individual weekly mean AM PEF. This figure displays the weekly means for AM PEF recorded daily on an asthma diary for each participant.

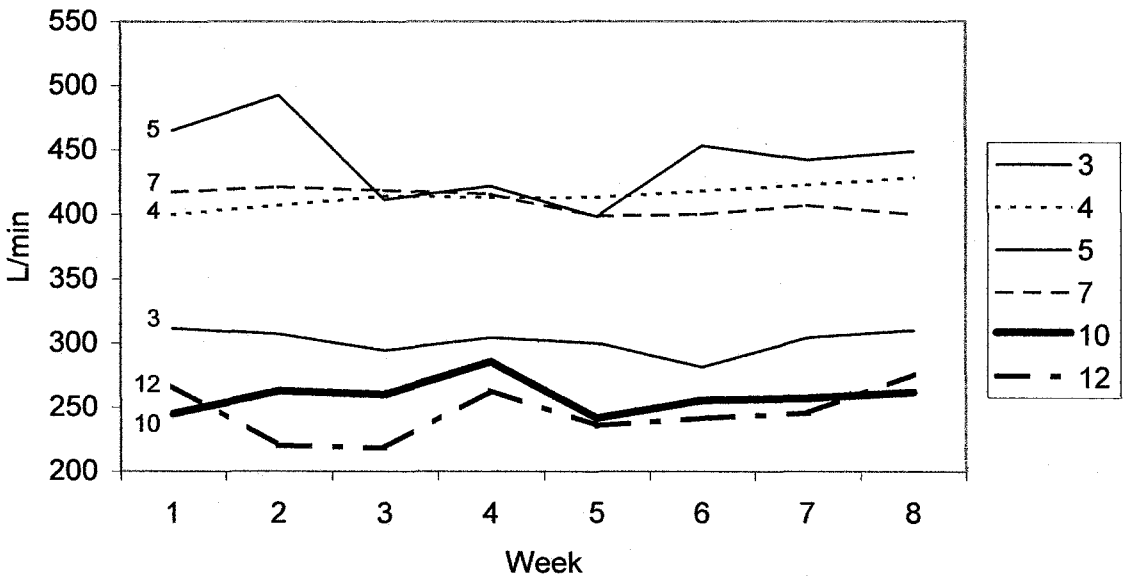

Figure 15. Referent group individual weekly mean AM PEF. This figure displays the weekly means for AM PEF recorded daily on an asthma diary for each participant.

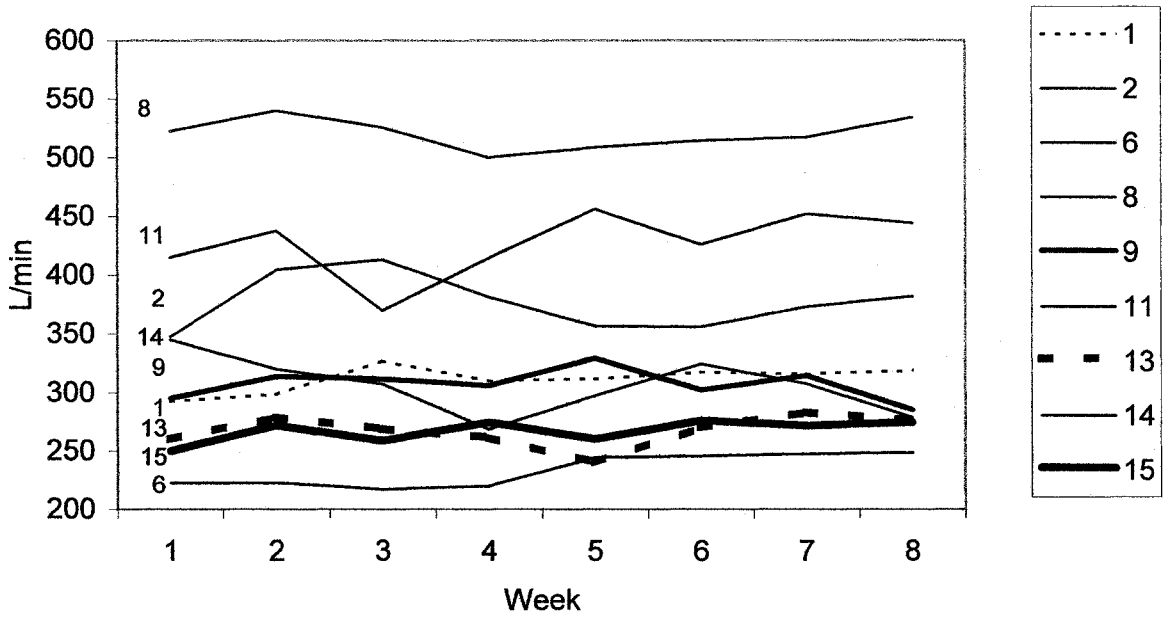

Figure 16. Treatment group individual weekly mean PM PEF. This figure displays the weekly means for AM PEF recorded daily on an asthma diary for each participant.

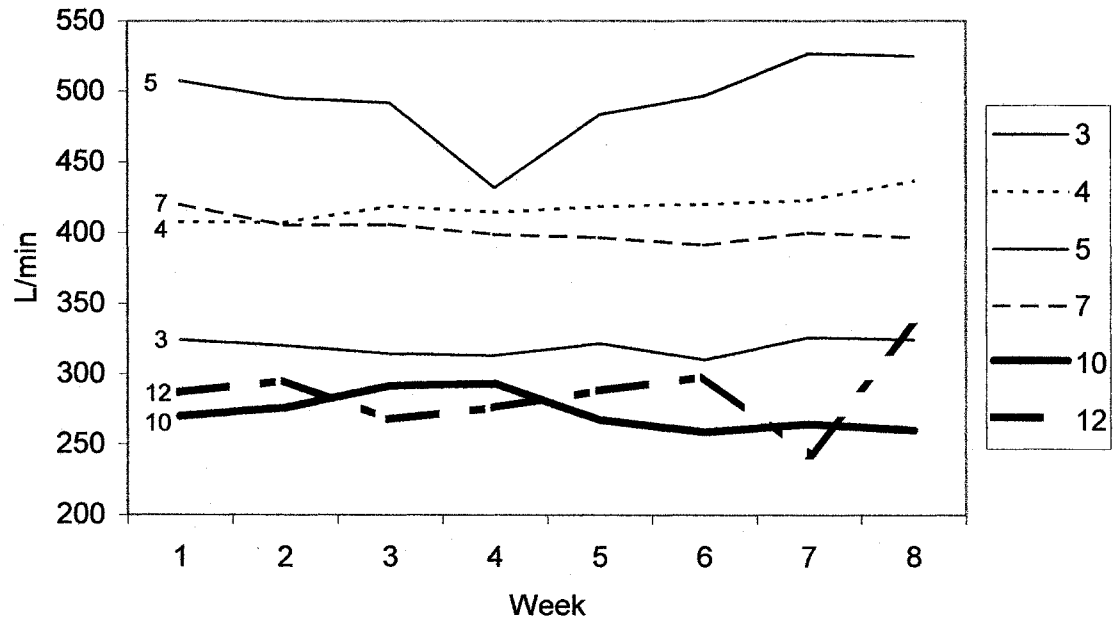

Figure 17. Referent group individual weekly mean PM PEF. This figure displays the weekly means for AM PEF recorded daily on an asthma diary for each participant.

There were trends of decreasing AM PEF in the treatment group, but slight decreasing trends are seen with participants 7 and 5 in the referent group. Individual trends in AM, PM, and weekly best PEF are also noted in Tables 8 and 9 in the presentation of clinical improvement later in the results section.

Individual weekly mean PM PEF for the treatment group also had a large degree of variability (Figure 16). There are no clear large trends in the data. Small trends of improvement can be observed for participants 11, 1, and 6. Participant 14 appears to have had a slight trend of decreasing mean PM PEF. In Figure 17 participant 4 from the referent group had a small trend of improvement in weekly mean PEF and participant 7 and 10 had small decreasing trends. Although Participant 5 increased to slightly above the level at week 1 after a large decrease mid-study, there is no clear trend. Participant 12 appears to have a slight trend of increasing PM PEF with some exacerbation in weeks 3 and 7.

Weekly best PEF. I also examined weekly best PEF to see if there were any clear trends in the data (Figure 18). Weekly best PEF was calculated by determining the highest AM or PM PEF readings during each week for each participant. The weekly mean for each group was calculated from this data. Mean weekly best PEF for the treatment group improved in the second week, decreased slightly in weeks 3 and 4 then increased in weeks 5 and 6. The treatment group mean decreased in weeks 7 and 8 but remained above the levels attained in weeks 2 through 5. Weekly best PEF for the referent group showed some variability, but there was little overall change.

It is easier to see the clinical importance of weekly best PEF data when it is displayed in terms of percent change from baseline (Figure 19). While we do not have a true baseline in this study, it is appropriate to consider week 1 as a baseline because most participants did not have their first treatment session until at least the 4th day of week one. Any treatment effects occurring in the first week are likely to have been small. The treatment group overall had a steady improvement in weekly best PEF while the referent group overall had no change.

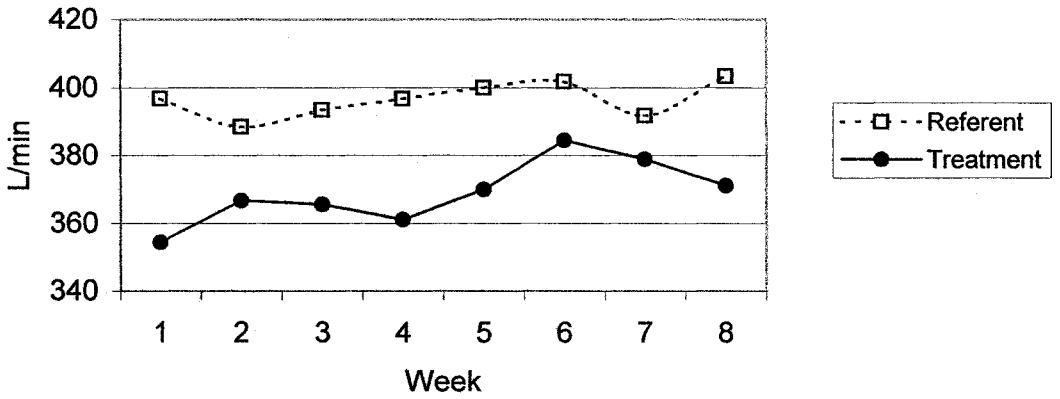

Figure 18. Weekly best PEF. Weekly best PEF was determined from AM and PM PEF recorded daily on an asthma diary by each participant. Each participant's weekly percent change from baseline (week 1) was used to calculate the group means. These individual bests were used to calculate the group means for each week of the study.

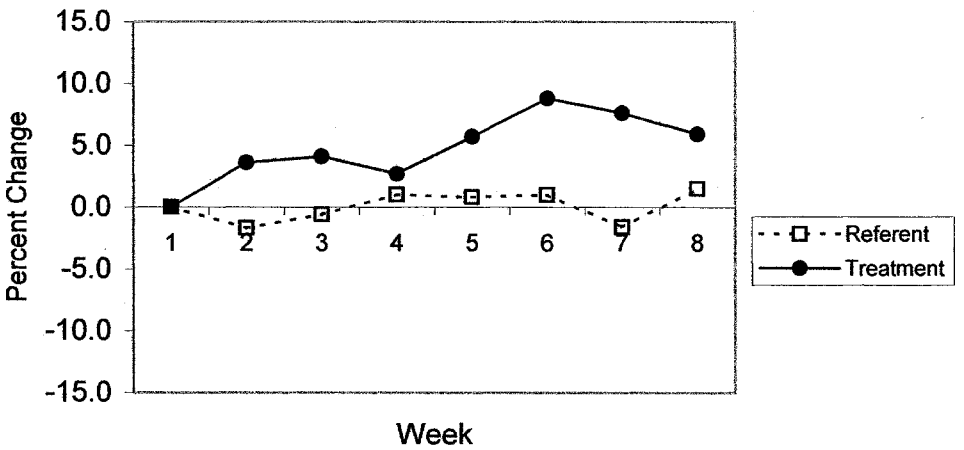

Figure 19. Weekly best PEF percent change. Weekly best PEF was determined from the highest weekly AM and PM PEF recorded on an asthma diary by each participant. Each participant's weekly percent change from baseline (week 1) was used to calculate the group means. These individual bests were used to calculate the group means for each week of the study.

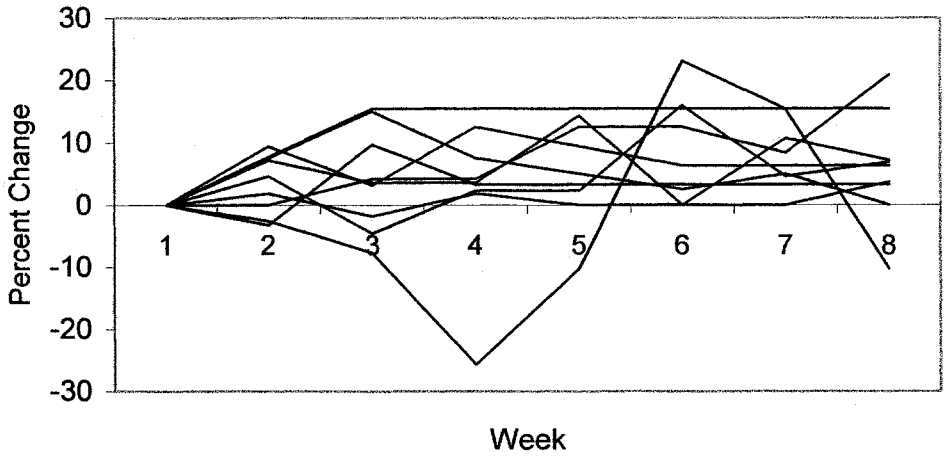

Figure 20. Treatment group individual percent change in best weekly PEF. Each participant's highest AM or PM PEF in week one was used as a baseline value for comparing weeks 2 through 8.

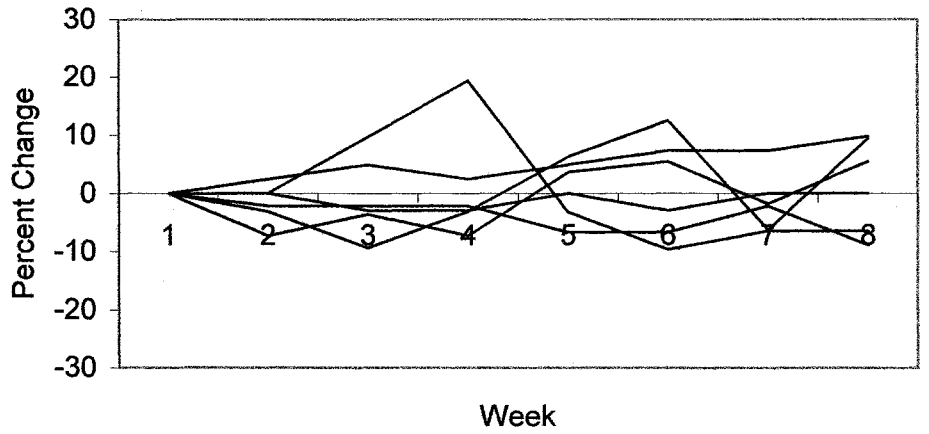

Figure 21. Referent group individual percent change in best weekly PEF. Each participant's highest AM or PM PEF in week one was used as a baseline value for comparing weeks 2 through 8.

Table 6.
Percent Change in Best Weekly PEF.

		Week							
Group	Subject	1	2	3	4	5	6	7	8
Treatment	1[ab]	0	-3.2	9.7	3.2	3.2	3.2	3.2	3.2
	2	0	7.5	15	7.5	5	2.5	5	0
	6[b]	0	4.2	4.17	12.5	12.5	12.5	8.3	20.8
	8[a]	0	1.8	-1.8	1.8	0	0	0	3.6
	9[c]	0	9.3	3.1	12.5	9.4	6.2	6.2	6.2
	11	0	4.5	-4.6	2.3	2.3	15.9	4.5	6.8
	13[b]	0	7.1	3.6	3.6	14.3	0	10.7	7.1
	14[c]	0	-2.6	-7.7	-25.6	-10.3	23.1	15.4	-10.3
	15[ab]	0	7.69	15.4	15.4	15.4	15.4	15.4	15.4
Referent	3	0	0	-2.9	-2.9	0	-2.9	0	0
	4	0	2.44	4.9	2.4	4.9	7.3	7.3	9.8
	5[a]	0	-7.3	-3.6	-7.3	3.6	5.4	-1.8	5.4
	7	0	-2.2	-2.2	-2.2	-6.7	-6.7	-2.2	-8.9
	10[b]	0	0	9.7	19.3	-3.2	-9.7	-6.4	-6.4
	12	0	-3.1	-9.4	-3.1	6.2	12.5	-6.2	9.4

Note. Each participant's highest PEF recorded in week 1 was used as the baseline value.
[a]Long acting bronchodilators (e.g., Salmeterol or Formeterol) used daily.
[b]Theophylline class long acting bronchodilator used daily.
[c]Short-acting bronchodilators were used daily prior to administration of inhaled corticosteroid.

Each participant's change in best weekly PEF is displayed in Figures 20 (treatment group) and 21 (referent group). The first week was used as a baseline value for comparing weeks 2 through 8. Although it is difficult to follow each participant's changes when viewed in the same chart, it is useful to compare the trends for each group. Using different line patterns to identify individuals on these charts was difficult because of the high degree of line overlap. Instead, the individual data used to create these charts is presented in Table 6.

Overall, it appears that the treatment group had greater improvements in best weekly PEF than the referent group. Consistent with weekly mean PEF data, there is a lot of variability in the weekly best PEF data. The most notable trends in improvement that were maintained during the study occurred with participant 6 and 15 in the treatment group and participant 3 in the referent group. Participant 6 gradually improved to 20% above baseline in week 8, and participant 15 improved 15% by week three and maintained that level of improvement through the remaining weeks of the study. Improvements for participants 6 and 15 occurred despite use of long-acting bronchodilators. Participant 14 in the treatment group varied from -25.6% at week 4 to 23.6% and 15.4% at weeks 6 and 7. Even with the large increase in weekly best PEF there is no clear trend. Participant 4 in the referent group had a gradual improvement, increasing 9.8% above baseline by week 8. The overall greater improvement seen in the treatment group is consistent with improvements in PEF, FEV_1, FVC, and FEF_{25-75} obtained by spirometry. Trends of slight decreases in best PEF occurred with participant 2 in the treatment group and 7 in the referent group. Although participant 10 in the referent group increased 19% in week 4, there was a downward trend to -6.4% in weeks 7 and 8.

Symptom Data

Participants recorded the overall level of severity of symptoms each day in 8 symptom categories, including wheeze and chest tightness. The ratings for each symptom were treated as continuous data and were totaled for each day of the study producing a daily total symptom score. The mean total symptom for each week of the study was calculated for each participant (Table 7). A repeated measures analysis of the

treatment * time interaction was not statistically significant ($F = 1.787$, $p = 0.14$). Power was calculated to be 52%. A between-group comparison of changes in weekly group means (Figure 22) will be presented first. A discussion of individual trends referring to Table 7 will follow.

Visual interpretation of changes in group means in Figure 22 reveals that the treatment group had an overall slight decrease in symptoms after some variability in weeks 2 and 3. The referent group had an increase in symptoms in weeks 2 and 3 then showed a notable decrease in symptoms in weeks 4 through 8. Individual symptom severity and trends can be seen in Table 7. There was a substantial range in the severity of symptoms experienced by participants. Participants 9, 3, and 4 were relatively symptom free and recorded an average total symptom score in 0-2 range. An average total symptom score of 1 means that on average they experienced mild symptoms in only one symptom category. Others had substantially more symptoms on a daily basis. Interpretation of symptom data must be approached with caution as symptoms are effected by the use of long-acting bronchodilators, short-acting bronchodilators, and reactions to environmental factors (e.g., allergens, irritants, air quality and temperature, psychological stress, and physical exertion). Visual interpretation of trends is subjective but still useful in understanding how individuals responded to the treatments. Trends for decreased symptoms in the treatment group occurred most notably with participant 6 which decreased from approximately 5 in week 1 to a score of 1 in week 8. Smaller trends of decreased symptoms occurred with participants 1, 8 and 9. Large decreases in symptoms occurred with participants 10 and 12 from the referent group. Smaller trends of decreased symptoms occurred with participants 5 and 7. It is difficult to interpret trends in data that is more variable (e.g., participants 2 and 4). Overall, the referent group had more symptoms than the treatment group at the beginning of the study and had a greater decrease in symptoms over the 8-week treatment period. This is not consistent with spirometry and daily PEF data. Participant 11 from the treatment group had a notable increase in symptoms in weeks 3 and 4 but returned to the level of symptoms at the beginning of the study (mean total symptom score of 0). Neither group had any individuals who reported increases in symptoms throughout the study.

Table 7.
Mean Daily Total Symptom Score.

		Week							
Group	Subject	1	2	3	4	5	6	7	8
Treatment	1[ab]	6.4	5.9	6	6.1	6.3	6.1	5.7	5.6
	2	3.4	4.1	5.6	2.9	4.4	4.1	4.1	2.5
	6[b]	5.1	3.9	2.7	2	1.9	3.7	1.7	1
	8[a]	6.7	4.7	5.6	5.6	5.4	5.3	5.1	5.3
	9[c]	1.9	2.4	1.9	1.7	1	1.1	1	1
	11	0	0.4	8.4	6.1	1.4	1.1	0	0
	13[b]	3.9	2.6	2.1	5	4.3	4.3	3.3	4
	14[c]	3.6	3.1	3.1	3	3	3	3.1	3
	15[ab]	5.3	4.1	4.1	3.9	6.2	6	7.6	4.9
Referent	3	0	0.9	0.4	0	1.3	0.1	0	0
	4	1.6	1.1	1.4	1.4	2.7	2	1	0.5
	5[a]	3.6	5.9	5.3	6	4.3	1.9	2.1	1.1
	7	11.4	11.4	11.7	8.6	11.6	8.4	8.4	8.4
	10[b]	11	9.4	11.3	12.6	8.9	8	9.3	4.8
	12	6.7	10.3	9.9	5.4	4.9	5.6	4.9	4.1

Note. This table shows the mean daily total symptom score for each week of the study. Severity of 8 different symptoms, including wheeze and chest tightness, was rated on a 5-point scale. 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe, 5 = required medical attention.

[a]Long acting bronchodilators (e.g., Salmeterol or Formeterol) used daily.

[b]Theophylline class long acting bronchodilator used daily.

[c]Short-acting bronchodilators were used daily prior to administration of inhaled corticosteroid.

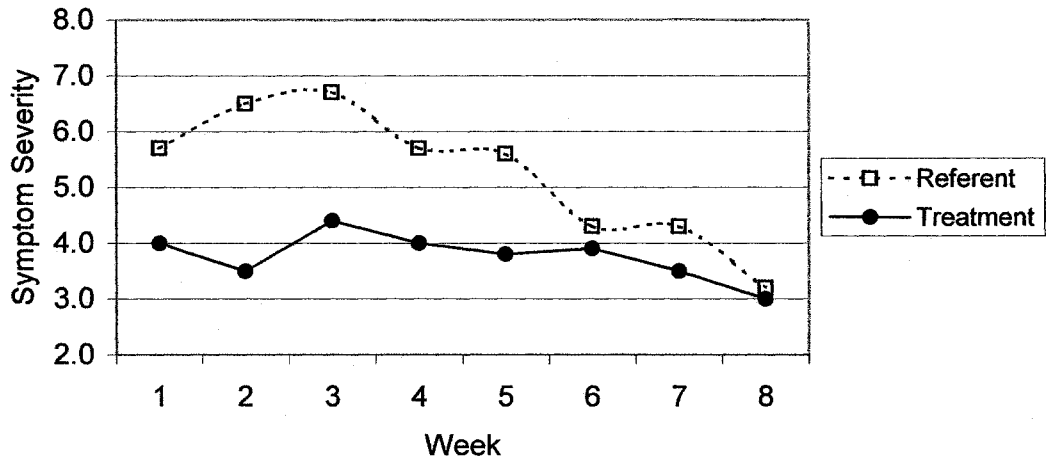

Figure 22. Total symptom scores. Group weekly means of asthma symptom severity were calculated from daily total symptom scores. Daily total symptom score = sum of severity ratings on 8 categories of asthma symptoms using a 5 point scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe, 5 = required medical attention). Repeated measures analysis of the treatment * time interaction was not statistically significant ($F = 1.787$, $p = 0.14$). The scale used in this figure should be interpreted as continuous scale and does not directly correspond to the 5-point scale.

Use of Reliever Medications

Use of asthma reliever medications (short-acting bronchodilators) was recorded on the asthma diary. All participants had been prescribed salbutamol (Ventolin) by their physicians with the exception of participant 1 who used terbutaline sulfate (Bricanyl). While some participants used reliever medication daily, many used reliever medication infrequently or rarely. Each participant's average daily use of reliever medication (number of times required) during each week of the study period was calculated. A repeated measures analysis revealed that the treatment * time interaction was not statistically significant ($F = 0.313$, $p = .873$). Very low power (12 %) was likely due to the low base rate caused by the infrequent use of the medication. With very low power, the result is inconclusive. Therefore, it is more appropriate to explore the trends for individual participants than presenting the group means.

Distinct trends in reliever use can be seen in several participants in Table 8 which shows the total number of times reliever medication was required each week. Participants 6, 8, and 9 in the treatment group had large reductions in medication use. Participant 8 had some missing data points in Week 8 because they stopped entering diary data prematurely due to an error made by a research assistant. However, considering the trend seen in the preceding weeks it is likely that no or only minimal reliever medication was used in week 8. Participants 1 and 15 in the treatment group also had reductions in use by week 8 despite increased use in the middle of the study. Participant 12 in the referent group had a large reduction in medication use. Participant 7 used reliever medication infrequently at the beginning of the study and did not require any in the last 4 weeks. However, the apparent trend is less convincing due to the small values in week 1 and 2 (medication required only 1 or 2 times). Participant 5 had a substantial increase in medication use during the middle of the study. Medication use in week 8 (2 times) decreased below use in week 1 (4 times). However, there does not appear to be a clear trend of decreased medication use. Although reliever medication was not used frequently enough by all participants to facilitate a between-group statistical comparison, visual analysis of trends was quite revealing. Dramatic reductions in reliever medication use

Table 8.
Number of times reliever medication was required each week.

		Week							
Group	Subject	1	2	3	4	5	6	7	8
Treatment	1[ab]	4	6	9	3	4	4	3	2
	2	0	0	2	0	6	2	3	0
	6[b]	29	28	25	22	16	20	10	15
	8[a]	4	7	7	6	0	0	0	0
	9[c]	6	2	2	4	2	2	1	0[d]
	11	0	5	19	16	6	8	1	2
	13[b]	27	25	26	29	27	30	26	31
	14[c]	11	14	12	15	12	10	9	11
	15[ab]	7	14	11	8	8	6	5	3
Referent	3	0	0	1	0	2	0	0	0
	4	0	0	1	0	1	1	0	0
	5[a]	4	9	9	16	18	7	7	2
	7	2	1	4	1	0	0	0	0
	10[b]	14	16	16	19	16	17	21	14
	12	16	19	20	11	2	2	4	2

Note. Table displays the total number of times reliever medication (short-acting bronchodilators) were required each week. Self-report data recorded on asthma diary.
[a]Long acting bronchodilators (e.g., Salmeterol or Formeterol) used daily.
[b]Theophylline class long acting bronchodilator used daily.
[c]Short-acting bronchodilators were used daily prior to administration of inhaled corticosteroid. As the dosage was stable during the study, only additional short-acting bronchodilator use was included in this table.
[d]Participant 9 only had 2 diary entries for week 8 due to a research assistant error.

occurred in 3 members of the treatment group and 1 in the referent group. Smaller reductions were noted in 2 members of the treatment group and 1 in the referent group. Overall, it appears that a larger proportion of the treatment group had reductions in reliever medication use. This interpretation is consistent with improvements in spirometry and weekly best PEF presented earlier. None of the participants reported large trends of increases in use of reliever medication, although participant 11 in the treatment group and 5 in the referent group had increased use in the middle of the study.

Clinical Improvement

Evaluating effectiveness of treatment for asthma by comparing changes on a single outcome measure has important limitations, especially with low power common to small trials. Clinical assessment of asthma involves the interpretation of multiple measures of lung function because the clinical picture for each patient may vary substantially. The various measurements obtained in a forced expiratory maneuver (FEV_1, FVC, FEF_{25-75}, PEF) reflect different aspects of lung function. It is not expected that any participants will show improvement in all of these measures. Clinically, if a patient has a notable change in only one of these measures, it represents an improvement in asthma. For example, a patient may have a clinically relevant increase in FEF_{25-75} and only a minor change in FEV_1. This patient's clinical improvement would not be reflected in a between-groups analysis of FEV_1. Similarly, clinical improvement that occurred in post-bronchodilator FEV_1 would not be reflected in a between-group analysis of pre-bronchodilator FEV_1.

In this section I will evaluate each participant's individual progress using clinically relevant cutoffs. If an individual participant had a clinically relevant improvement over the course of the study they will be classified as responders. Initially, interpretation of clinical change will be limited to data obtained by spirometry. Changes in the daily measurements of PEF will then be evaluated. Consistency with changes in use of reliever medication and symptom scores will be discussed. Finally, spontaneous anecdotal comments made by study participants referring to asthma and non-asthma benefits from the treatments will be reported.

Clinical Cutoffs

Clinical cutoffs were defined as the minimum improvement over time that is beyond normal variability in measures of lung function. Most guidelines define the amount of change in a measure of lung function that is required to establish the diagnosis of asthma or determine a response to bronchodilator therapy. Boulet et al. (1999) recommended a 20% improvement in FEV_1 or serial measures of PEF over time for the diagnosis of asthma. The American Thoracic Society (1991) recommended using changes of 11% in FVC, 12 % in FEV_1, and 21% in FEF_{25-75} with normal subjects as a cutoff for a significant change from week to week. Meaningful year-to-year change should be at least 15 % change in FEV_1. An established cutoff relevant to this study is the 15% improvement in FEV_1 or PEF after treatment with oral prednisone for 2 weeks used to determine if a patient either responded to the treatment or has corticosteroid-resistant asthma (Barnes, 1998).

Clinical improvement in the current study was defined as ≥15% increase in FEV_1, FVC, or PEF, and a ≥21% increase in FEF_{25-75}. Clinical improvement in each group is summarized in Table 9. Pre- to post-treatment changes for individual participants are shown in Table 10 (Treatment group) and Table 11 (Referent group). Trends in diary data presented earlier and anecdotal reports of important clinical changes discussed in the next section are also included in the tables for comparison.

While 7 out of 9 participants (78%) in the treatment group demonstrated clinical improvement in measures of lung function obtained by spirometry, none in the referent group reached the clinical cutoffs. Four of the responders (57%) improved in both pre- and post-bronchodilator spirometry. The remaining 3 responders (43%) showed clinically significant improvement in post-bronchodilator spirometry only. None of the responders showed a pattern of improving in pre-bronchodilator measures only. Clinical improvement was consistent with trends seen in diary data for 5 (71%) of the responders (participants 1, 8, 11, 14, and 15).

Table 9
Clinical Improvement in Lung Function: Crosstabulation of Responders with Group.

	Group		
Clinical Improvement	Treatment	Referent	Total
Improvement	7 (78%)	0 (0%)	7
No Improvement	2 (22%)	6 (100%)	8
Total	9	6	15

Note: Table shows count of participants with clinically significant treatment response (with proportion of each group in parentheses). Clinical response to treatment is defined as ≥15% increase in pre- or post-bronchodilator FEV_1, FVC, or PEF, and ≥21% increase in FEF_{25-75}. FVC = forced vital capacity. FEV_1 = forced expiratory volume in 1 s. FEF_{25-75} = mean forced expiratory flow between 25% and 75% of the expired vital capacity. PEF = peak expiratory flow.

Table 10.

Clinical Improvement in Lung Function and Diary Data: Treatment Group.

	Participant								
Measure	1[a]	2	6[a]	8[a]	9[a]	11	13[a]	14[a]	15[a]
Pre-bronchodilator									
FVC	4.2	0	-10.3	15.4	7.5	9.5	3.4	10.4	2.8
FEV1	2.6	5.8	-16.7	5.83	3.4	16.7*	0	25.5*	8.4
PEF	11.4	12.6	-18.2	13.9	-11.7	8.9	-4	39*	41.5*
FEF25-75	0.6	24*	-25	-22.1	-3.4	35.8*	2.3	-1.5	21.6*
Post-bronchodilator									
FVC	3.8	-4.8	-9.9	17.6*	-3.2	9.5	17.6*	17.3*	-1.2
FEV1	3.1	-2.3	-16.2	11	-1.7	19.2*	7	20.1*	5
PEF	16.2*	17.8*	-6.4	3.3	6.9	10.6	-11.7	15.3*	32.4*
FEF25-75	4.4	5.4	-20.4	-12.6	-0.5	45.6*	-12.1	25.4*	15.1
Treatment Response[b]	yes	yes	no	yes	no	yes	yes	yes	yes
Therapist[c]	a	a	a	b	c	d	c	a	a
Diary Data[d]									
AM PEF trend	↑	–	↑	⇑	–	–	–	–	–
PM PEF trend	↑	–	↑	–	–	↑	–	↑	–
Best PEF trend	–	↓	⇑	–	–	–	–	–	⇑
Symptoms	↓	–	⇓	↓	↓	–	–	–	–
Reliever medication use	↓	–	⇓	⇓	⇓	–	–	–	↓
Max Δ AM PEF[e]	8.8	9.8	10.4	13.7	-0.8	6.4	-0.8	-2.5	9.7
Max Δ PM PEF[e]	11.7	18.8	11.7	3.3	11.6	9.9	8.8	-6	10.3
Max Δ Best PEF[f]	9.7	15	20.8	3.6	12.5	15.9	14.3	23.1	15.4
Anecdotal Reports[g]									
Decreased "panic"		yes					yes		
Feeling of control	yes	yes					yes		
Relief of exacerbation					yes		yes	yes	yes
Decreased "stress"		yes							
Other health benefits		yes		yes					

Note: Table shows pre- to post-treatment change (%) in measures of lung function obtained by pre- and post-bronchodilator spirometry. [a]Long acting bronchodilators used daily. [b]Clinical response to treatment is defined as ≥15% increase in pre- or post-bronchodilator FEV_1, FVC, or PEF, and ≥21% increase in FEF_{25-75}. [c]Therapist A is the researcher, therapist B is the senior research assistant, and therapists C and D are research assistants. [d]Trends from diary data discussed earlier are included for comparison with spirometry. ⇑ or ⇓ = large trend. ↑ or ↓ = small trend. "–" = no visually apparent trend. [e]Maximum positive change in weekly means of daily morning (AM) or evening (PM) peak expired flow (PEF) measurements in Weeks 2 to 8 using Week 1 as baseline value. [f]Maximum positive change in weekly best PEF (AM or PM). [g]Anecdotal reports of decreased panic when without short-acting bronchodilator, feeling of control over asthma, control of short-term symptom exacerbation by use of imagery, decreased experience of life "stress", and positive side effects of improvement in non-asthma symptoms. Includes only anecdotal reports provided spontaneously as participants were not questioned about these experiences. *Clinically significant response to treatment.

Table 11.
Clinical Improvement in Lung Function and Diary Data: Referent Group.

	Participant					
Measure	3	4	5[a]	7	10[a]	12
Pre-bronchodilator						
FVC	-12	2.1	10.5	12.1	10.6	-4.5
FEV1	-16	-1.6	10.7	7.5	13.3	-11.8
PEF	-5.7	-2	12.4	2.5	-8.1	-6.9
FEF25-75	-22.5	-12.7	9	9.3	18.9	-6.8
Post-bronchodilator						
FVC	-3.6	0.3	-2.6	6.5	10.3	-0.6
FEV1	1.8	-3.6	-5.8	0.5	0.6	5.8
PEF	-10	-6.4	3.6	-2	-8.5	10.7
FEF25-75	6.7	-15.2	-7.1	-13.6	-3.7	17.3
Treatment Response[b]	no	no	no	no	no	no
Therapist[c]	a	a	a	a	c	b
Diary Data[d]						
AM PEF trend	–	↑	↓	↓	–	–
PM PEF trend	–	↑	–	↓	↓	–
Best PEF trend	–	↑	–	↓	↓	↑
Symptoms	–	–	↓	↓	⇓	⇓
Reliever medication use	–	–	–	↓	–	⇓
Max Δ AM PEF[e]	-0.4	7.1	5.9	0.9	16.6	3.5
Max Δ PM PEF[e]	0.4	7.2	3.8	-3.4	8.5	16.3
Max Δ Best PEF[f]	0	9.8	5.4	-2.2	19.3	12.5
Anecdotal Reports[f]						
Decreased "panic"	yes		yes			
Feeling of control			yes			
Control of exacerbation	yes		yes	yes	yes	
Decreased "stress"	yes		yes	yes		
Other health benefits			yes			

Note: Table shows pre- to post-treatment change (%) in measures of lung function obtained by pre- and post-bronchodilator spirometry. [a]Long acting bronchodilators used daily. [b]Clinical response to treatment is defined as ≥15% increase in pre- or post-bronchodilator FEV_1, FVC, or PEF, and ≥21% increase in FEF_{25-75}. [c]Therapist A is the researcher, therapist B is the senior research assistant, and therapists C and D are research assistants. [d]Trends from diary data discussed earlier are included for comparison with spirometry. ⇑ or ⇓ = large trend. ↑ or ↓ = small trend. "–" = no visually apparent trend. [e]Maximum positive change in weekly means of daily morning (AM) or evening (PM) peak expired flow (PEF) measurements in Weeks 2 to 8 using Week 1 as baseline value. [f]Maximum positive change in weekly best PEF (AM or PM). gAnecdotal reports of decreased panic when without short-acting bronchodilator, feeling of control over asthma, control of short-term symptom exacerbation by use of imagery, decreased experience of life "stress", and positive side effects of improvement in non-asthma symptoms. Includes only anecdotal reports provided spontaneously as participants were not questioned about these experiences. *Clinically significant response to treatment.

Two responders (29%) did not show improvements in diary data that would have been consistent with significant improvements in lung function. Participant #2 had no obvious trends of improvement in AM or PM PEF and a slight trend of decreasing weekly best PEF. However, PM PEF and best weekly PEF rose ≥15% above levels in week 1. Participant 13 had an increase in post-bronchodilator FVC but no obvious trends in diary data. This is a good example of an individual who had improvement in a post-bronchodilator measure of lung function but had no change in pre-bronchodilator measures or diary data. Persistent bronchoconstriction was a problem for this individual as is evident by the need for a long-acting bronchodilator. Participant 13 likely had decreased airways inflammation, as indicated by increased post-bronchodilator FVC, but had no notable change in bronchoconstriction during the study. However, as will be discussed later in the results section, this individual did report avoiding use of reliever medication by using imagery for immediate relief of symptoms.

Two participants in the treatment group, 6 and 9, did not improve to the established cutoffs for clinical improvement. Surprisingly, Participant 6 had clinically significant decreases in lung function despite large trends of decreased symptoms and reliever medication use, and increased weekly best PEF. Participant 6 also had small trends of increasing weekly mean AM and PM PEF. Possible reasons for the discrepancy include the use of a theophylline class long-acting bronchodilator (Theodur 300 mg) and environmental factors. The long-acting bronchodilator, which may have masked symptoms and decreasing lung function in the diary data, was withheld prior to performing spirometry. On the other hand, participant 6 complained of high humidity in the last treatment session and may have been at the beginning of an asthma exacerbation at the time of the second lung function assessment. If a ≥15%, or even a more stringent ≥20%, increase in diary data PEF was used as a criterion of improvement, participant 6 had a clinically significant improvement in weekly best PEF (20.8% increase in week 8) but not mean AM or PM PEF. As discussed earlier, one of the weaknesses of the diary data in evaluating clinical change was that the study design did not include a pre-treatment baseline. Instead, measures in week 1 are used as the baseline for comparing weeks 2 through 8.

None of the participants in the referent group reached the clinical cutoffs for improvement in measures of lung function obtained by spirometry. Participant 3 had a clinically significant decrease in lung function obtained by spirometry and no trends in diary data were observed. I will examine changes in the diary data of the referent group to determine if any clinically relevant improvements occurred. Participant 10 had improvement in PEF ≥15% in week 4 with nearly 17% increase in AM PEF and 19% increase in weekly best PEF. However, the overall trend in AM PEF, weekly best PEF, and symptoms was negative. The temporary increases in PEF Week 4 was likely due to increased use of short-acting bronchodilator medication during that week (see Table 8). Thus, the temporary increase in PEF for participant 10 did not accurately reflect clinical improvement. In contrast, the 16% improvement in PM PEF recorded in week 8 for participant 12 was consistent with trends in diary data. While there were no obvious trends in AM or PM PEF for this participant, there were large trends of decreasing symptoms and use of short-acting bronchodilator medication.

In summary, using pre- to post-treatment changes measured by spirometry, 7 out of 9 participants in the treatment group and 0 out of 6 in the referent group demonstrated clinically relevant improvements in lung function. One participant (#6) in the treatment group had a clinically significant decrease in lung function obtained by spirometry. A total of 4 participants in the referent group had clinical changes for the worse. One had significant decreases in pre- and post-bronchodilator spirometry and 3 had severe exacerbations that required medication change or hospitalization resulting in their withdrawal from the study.

This study was designed to utilize measures obtained by spirometry as the primary efficacy outcome variables. Diary data was collected as supportive data. However, trends in PEF measures recorded on the asthma diaries can also be used to evaluate clinical improvement. Diary data offers the advantage of multiple data points facilitating analysis of trends. As well, symptom severity ratings and medication usage data can be compared with changes in PEF to evaluate consistency of the self-report data. As discussed earlier, weaknesses of diary data include the influence on data of long-acting bronchodilators and poor compliance. If the PEF diary data is included in the evaluation

of clinical improvement, the number of participants who are considered to have responded to the treatment increases. Using a cut off of ≥15% improvement in PEF, one additional participant from each group is considered a responder to the treatments. While participant 6 from the treatment group had a significant decline in spirometry, there was a significant improvement in weekly best PEF and large positive trends in symptoms and use of reliever medication indicating a steady improvement throughout the treatment period. Thus, using both spirometry and diary data, 8 out of 9 participants in the treatment group and 1 out of 6 in the referent group had clinically relevant improvements.

Which therapists provided treatment to the participants is also illustrated in Tables 8 and 9. Each therapist had at least one participant who had a clinically significant improvement in lung function. This provides support to the assumption that the improvements are related to the treatment approach and not the characteristics of one researcher or therapist.

Anecdotal Reports of Improvement

Participants had an opportunity in each session to comment on their experiences during the previous week. For example, participants would report changes in their imagery, pose questions about the treatment process, and comment on changes in symptoms and PEF. Even though this was unstructured and no standardized questions were used, several themes emerged in these anecdotal reports: decreases in particularly bothersome asthma symptoms, decrease in "stress" and other non-asthma symptoms, use of imagery or relaxation to reduce symptoms during a brief exacerbation instead of using short-acting bronchodilator medication, decreased feeling of panic if they did not have their short-acting bronchodilator at hand (whether or not they were experiencing increased symptoms), and increased feeling of control over asthma. The occurrence of anecdotal reports in all theme areas except asthma symptoms are included in Tables 7 and 8 for comparison with changes in outcome measures.

The first theme is decreased asthma symptoms. Many participants reported decreased symptoms and most of this was reflected in the asthma diary data. However, for some participants a reduction in a particularly bothersome symptom appeared to be important to them in terms of quality of life. In the treatment group, participant 14

reported decreased hyperreactivity to cold air and had decreased mucus production. In session 4, participant 14 noted that the mucus from the lungs had become clearer rather than the brown color that was normal. Colored mucus may be due to the presence of cellular debris and other by-products of the inflammatory process. The change in mucus quality and quantity likely reflects a change in airway inflammation. Participant 15 had decreased daily tightness in throat that had sometimes interfered with speaking and reported increased comfort in breathing during a treatment session. In the referent group, participant 7 had less fatigue and participant 12 experienced decreased wheezing upon exertion.

It is interesting to note that participant 15 (who reported decreased throat tightness) did not have a significant improvement in FEV_1 or FVC but had substantial clinical improvement in pre- and post-bronchodilator PEF (41% and 32% respectively) and significant improvements in small airways (FEF_{25-75}). This improvement PEF (large airways) is consistent with decreased throat tightness. During the treatment period, this participant had been disappointed that dramatic improvements in symptoms and daily PEF were not apparent. This is an example of an individual for whom use of a long-acting bronchodilator may have masked changes in diary data. However, while there were no trends in weekly mean AM or PM PEF, there was a large trend of increasing weekly best PEF which is consistent with the anecdotal report of decreased throat tightness and significant increases in PEF obtained by spirometry. This provides support for the use of weekly best PEF as an outcome measure.

Some participants reported improvements in "stress" and other non-asthma symptoms. Participant 2 in the treatment group and participants 3, 5, 7, and 10 in the referent group reported reduced experience of daily stress and/or use of relaxation or imagery to cope with stress. In the treatment group, participant 2 also reported a cessation of headaches (previously 2-3 per week) and participant 8 was sleeping better with less mental "chatter". In the referent group, participant 5 reported less stomach upset.

One important area not assessed by the asthma diary is subjective feelings of control over the disease. Three themes of anecdotal reports appear to be interrelated: use

of imagery or relaxation to obtain immediate symptom relief instead of using a short-acting bronchodilator medication, decreased feeling of panic if they did not have their short-acting bronchodilator at hand (whether or not they were experiencing increased symptoms), and specific statements that they feel increased control over asthma. Having the experience of controlling an asthma attack without relying on medication may lead to a feeling of decreased dependence on reliever medication and decreased panic without the medication (e.g., if an individual forgets their Ventolin at home). However, the decreased panic and feeling of control could occur without the experience of immediate relief following imagery or relaxation practice. Decreased panic at times without a bronchodilator and experiences of immediate symptom relief (and thus removing the need for bronchodilator) can both be interpreted as examples of increased feeling of control over the disease.

Four participants in the treatment group reported using asthma specific imagery to gain symptom relief at times of exacerbation. Three out of these (9, 13, and 14) used imagery to gain symptom relief and avoid using reliever medication. Participant 15 also reported decreased tightness within a "couple" minutes of using imagery but did not specify if use of reliever medication was avoided. Three participants in the referent group (3, 5, and 7) reported avoiding use of reliever medications in a similar fashion, although it is not clear if they used relaxation imagery or a form of physical relaxation. For example, participant 7 included positive self-talk and slow deliberate breathing in the attempt to decrease symptoms. Participant 10 in the referent group reported using relaxation imagery to decrease stress related asthma symptoms, but did not comment on medication use.

It should be stressed that to my knowledge none of the participants were asked specific questions about these theme areas, e.g., if they used the imagery instead of ventolin. Therefore, only participants who felt it was important to mention would have reported this information. Other participants may have had similar experiences but failed to report it. Although the research assistants were encouraged to record any anecdotal reports, I cannot ensure that all reports were recorded as it was not a structured part of the treatment protocol. Therefore, it is inappropriate to make between-group comparisons on

these anecdotal reports. It is appropriate to conclude that some members of both groups reported decreased feelings of panic when without their reliever medication, used imagery and/or relaxation to decrease symptoms and avoid use of reliever medication, felt increased control over the disease and decreased stress, and reported non-asthma health benefits. All members of the treatment group that used their new skills to avoid using reliever medication used asthma specific imagery. Individuals in the referent group who also found they could voluntarily decrease their symptoms appear to have used different combinations of imagery, relaxation, self-talk, and controlled breathing.

In summary, 7 participants in the treatment group provided anecdotal reports of asthma and non-asthma benefits related to the treatment. One of those who reported immediate symptom relief and avoidance of reliever medication showed a large trend in decreased use of reliever medication but no clinically significant improvement in lung function (participant 9). Although improvements in spirometry for the referent group were not large enough to reach clinical significance, 4 participants reported anecdotal improvement. One of these, participant 3, reported decreased panic and stress and increased control of exacerbations despite a significant decrease in lung function.

CHAPTER 5: DISCUSSION

Discussion of Results

This study was carefully designed to address the question of the effectiveness of immune specific imagery to increase lung function in adults with asthma, and control multiple treatment factors to determine if treatment effects are related to the process of imagining immune system changes or other components of the treatment such as relaxation. The finding of a statistically significant difference between the groups, even if only marginal, is interesting and provides some support for the hypothesis. However, this was a pilot study with low power and multiple tests were conducted. After adjusting for multiple testing the one significant interaction was not longer statistically significant.

As discussed below, the findings suggest that the inflammatory processes in asthma can be modulated by immune specific mental imagery. As well, it appears that by virtue of decreased inflammation or other unknown mechanism the treatment may have a protective effect against respiratory infections. Both treatments studied provided some relief from bronchoconstriction but relaxation therapy combining progressive relaxation with calm scene imagery did not appear to significantly reduce airway inflammation.

The finding of a statistically significant difference between the groups is rather remarkable considering the goal of the study required the comparison of two very similar psychological treatments. The study was designed to find effects that are specific to type of mental imagery incorporated into the treatment. Only treatment effects incremental to factors common to imagery treatments such as physiological relaxation and practice of imagery, and incremental to factors common to most psychological treatments (e.g., expectation for improvement, attention, understanding, etc.) would be revealed. Many studies and meta-analyses comparing psychological treatments found little or no difference between therapies (Lambert & Bergin, 1994). This is not because the treatments were ineffective, or that there are no clinically important differences between the treatments, but that their similarity makes it unlikely to find a statistically significant difference between them even in large trials. Even with potent pharmaceuticals, only small effect sizes are expected with comparisons of treatments for asthma (Richards & Hemstreet, 1994). As no medication withdrawal phases were incorporated into the design

of the current study, participants had to improve over and above current medical treatment, which is very effective at suppressing airway inflammation. All participants received inhaled corticosteroids and many used long-acting bronchodilators.

The findings suggest that imagery representing modulation of the inflammatory mechanisms of asthma does modulate airway inflammation in some manner. Between-group analysis and examination of changes at an individual level revealed that the treatment group improved in both pre- and post-bronchodilator measures of lung function with greater changes post-bronchodilator. Post-bronchodilator measures are indicators of airway narrowing due to inflammation and represent the best lung function that can be achieved with bronchodilator therapy. If only pre-bronchodilator measures of lung had improved, then the treatment may have only affected bronchoconstriction.

Although lung function did not improve overall for the referent group, some participants in the referent group felt that they benefited from practicing relaxation and reported decreased symptoms and anecdotal benefits such as decreased panic. Four participants in the referent group reported the ability to control exacerbations and avoid use of reliever medication. Three of the four participants had moderate but non-clinically significant improvements in pre-bronchodilator lung function but little change in post-bronchodilator measures. It appears that for some individuals, relaxation training provided slight benefit in reducing bronchoconstriction in the long-term and facilitated increased control over short-term exacerbations. However, as relaxation imagery did not significantly improve lung function, relaxation likely did not decrease airway inflammation to a clinically relevant degree. In contrast, those who practiced immune modulating imagery improved in both large and small airway functioning in pre- and post-bronchodilator measures. Some of the participants in the treatment group also reported the ability to control exacerbations using asthma specific imagery, indicating that the treatment can decrease bronchoconstriction as well as airway inflammation.
I speculate that in addition to modulating airway inflammation the treatment imagery somehow effects one or more of the neuronal or biochemical processes associated with constriction of airway smooth muscle. Perhaps the treatment can modulate cholinergic or adrenergic activity. Considering that treatment effects occurred in both airway

inflammation and bronchoconstriction, there is no apparent benefit to using relaxation imagery instead of or in addition to the asthma specific treatment imagery.

The extremely variable nature of asthma makes it a difficult disease to study. Individuals with asthma are more susceptible to colds and respiratory infections, which exacerbate airway inflammation and decrease lung function. Multiple environmental variables such as air quality and seasonal allergens influence degree of bronchoconstriction and inflammation. In this study, participant 6 in the treatment group had large trends of decreased use of reliever medication and symptoms and clinically significant improvements in daily PEF. However, pre- and post-treatment spirometry showed decreased pulmonary function. This individual complained of high humidity toward the end of the study. Others complained of smoke from forest fires, allergens, and changes in air temperature. Smoke from forest fires may have played a role in the exacerbation and subsequent withdrawal of one of the participants. Stress related exacerbations were also reported. Extraneous variables increase the probability that research participants will not remain stable and will suffer decrements in lung function during a study. While there were no respiratory infections documented in the treatment group, three participants from the referent group were withdrawn due to respiratory infections requiring medication changes. Epithelial damage, mucociliary impairment, and other consequences of airway inflammation increase the risk of respiratory infection. I speculate that as a result of decreased airway inflammation and/or other unknown treatment effects; immune modulation imagery may have served as a protective factor, decreasing the incidence of respiratory infections. This hypothesis should be tested in a larger clinical trial.

Strengths and Limitations of the Study

This was a pilot study and as such has a number of weaknesses and limitations. However, it has numerous strengths that increase the importance of the results and broaden the generalizability of the findings. One of the most important strengths of the study is the design. Originally I had proposed to compare the immune imagery treatment to a control group receiving only standard medical care. This was wisely challenged in my candidacy committee as it was pointed out that a significant finding with this design

would not isolate the relevant aspect of the treatment, namely the imagery representing immune modulation. Thus, I designed a study that controlled for all aspects of the treatment except the type of images practiced by the participants. A negative aspect of this new design was that the treatments would be so similar it was much less likely that a significant result would be found, particularly with the small sample size dictated by limited resources. However, a significant finding with the revised design would have much greater implications for the theories of mind-body healing, clinical practice, and future research.

It will be difficult to argue that the benefits of the treatment were due to a placebo effect. Boulet et al. (1999) stated that improvements observed with unconventional therapies (including hypnosis) are no different from placebo effects and that positive results in uncontrolled studies are explained by the placebo response. The current study is a randomized controlled study that used a valid psychological treatment (relaxation imagery) as the control. Since relaxation was an active treatment and not a true placebo control, I have referred to it as the 'referent' treatment rather than 'control.' All participants were told that they were learning a real psychological treatment that they were expected to benefit from and that the purpose of the study was to determine if one of the treatments was more "powerful" than the other. Relaxation appeared to have a high degree of face validity as a treatment for asthma. I have observed an almost universally positive response among asthma patients and laypersons, and even some medical professionals, when they hear that the study somehow involves relaxation. It appears to be common knowledge that decreasing "stress" is beneficial to asthma patients. However, many people are unaware of the use of imagery to influence the immune system in research or clinical practice.

An approximately equal number of participants withdrew themselves from each group for unspecified reasons. To my knowledge none of the participants in the referent group questioned the validity of the treatment. I recall that one participant in the referent group did enquire about using imagery related to asthma as an alternative to relaxation imagery, but they still appreciated the value of relaxation as a treatment and were not reluctant to continue. It might be argued that asthma specific imagery may have more

face validity and therefore those in the treatment group may have had a stronger belief in its efficacy. However, based on the interest and enthusiasm displayed by participants, it is my impression that differences in efficacy beliefs would be minimal. Practically, it would be difficult to design a referent treatment that would reduce differences in efficacy beliefs more than the current study.

Boulet et al. (1999) acknowledged that the findings of open and single-blind studies have suggested a role of relaxation techniques or hypnosis in the treatment for asthma but then criticized that no well controlled double blind studies have adequately examined these therapies. It is likely that all research of psychological treatments could be dismissed with this argument. Unlike pharmaceuticals which can easily be disguised, the training of skilled therapists in the psychological treatments under study cannot be disguised. 'Blind' designs in psychological research are rarely possible and the validity of psychological placebo 'treatments' has been questioned (Anthony, 1993). While the current study is subject to Boulet et al's criticism the standard of double blinding in medical research is not practically achievable in the study of this treatment. Thus, the results should not be dismissed. Instead, the study should be replicated with a larger sample and an additional control group.

It may be argued that the group practicing relaxation imagery may have become more deeply relaxed than the immune imagery group. I cannot present data to address this issue, as physiological indicators of relaxation were not measured. However, my clinical observation was that there was no notable difference in depth of relaxation achieved with the two treatments. Participants in both groups reported moderate to deep levels of physiological relaxation. It is important to remember that a passive progressive relaxation induction was used with both treatments. The imagery process in both treatments was active rather than passive. Each participant generated their own imagery and was required to switch between images and make an effort to alter their imagery to make it more 'powerful.' Thus, I propose that the treatment conditions were very similar in terms of relaxation effects and active mental process.

Hall et al. (1995) speculated that changes in neutrophil adhesion might have been related to the process of intervention. Specifically, that decreased adhesion may be

related to "active- imaging" while increased adhesion may be related to "passive-resting". If, as I propose, both treatments in the current study involve "active-imaging" then the level of activity involved in the treatment should be relatively controlled between the groups. Thus, differences in level of activity between the treatments is not an adequate explanation for the difference in treatment response between the two groups. It is more likely that the treatment effects are related to the type of imagery practiced.

Although additional outcome measures could have been utilized, the current study is a notable improvement over the vast majority of studies of psychological treatments for asthma. Most studies have used spirometry or diary data, but not both. I do not recall any studies that used both pre- and post-bronchodilator spirometry. The results of the current study illustrate the importance of post-bronchodilator measures in the research of psychological treatments for asthma.

The use of research assistants as therapists was a strength of this study. The observation that treatment response was not associated with only one therapist is evidence that the treatment effect is related to the treatment rather than the characteristics of one therapist. However, training for the therapists should have been more extensive. Procedures should have been developed to evaluate competence of the therapists and reliability of treatment delivery. It is possible that attrition could have been reduced and the treatment could have been more effective with improved therapist training. As well, the research assistants should have been involved from the outset of the study and their assignment to participants should have been randomized.

The results of this study are generalizable to adults with males and females with moderate to severe asthma between the ages 18 and 70 receiving treatment with daily doses of inhaled corticosteroids. Recruitment from a variety of sources, including public advertising, family physicians, and two asthma hospital clinics broadens the population that the results can be generalized to. Many of the participants were using long-acting bronchodilators and response to treatment did not appear to be different for these individuals. Even with daily use of long-acting bronchodilators, individuals in both groups provided anecdotal reports of using the treatments to decrease symptoms during exacerbation and avoid the use of reliever medication. Although the majority of

participants were atopic, individuals with non-atopic and occupational asthma also responded to treatment.

In Zukiwski (1996), a participant with non-atopic occupational asthma who was on a stable dosage of oral prednisone for years prior to and during the study had clinically significant improvements in lung function and symptoms. This individual contacted me after the study to report that his pulmonologist discontinued the prednisone because of the gains in lung function made during the study. This was an important improvement in quality of life as he had experienced notable weight gain as a side effect of the prednisone. Although neither study was designed to evaluate treatment efficacy for occupational or non-atopic asthma, it appears that the treatment may also benefit these populations. If only atopic individuals responded, then the treatment might be effecting only the allergen-antibody complex. As non-atopic and occupational asthma responded, the treatment appears to effect other aspects of the inflammatory process.

One of the greatest limitations of this study is the small sample size and high attrition. The low power in the analysis increased the probability of a Type II error. Participant withdrawal may have effected group composition. Balance in potentially confounding variables was analyzed before and after attrition and no statistically significant differences were found. However, there may be unknown characteristics in those withdrawn that may have interacted with the treatment in some manner.

Although the referent group was used to isolate the effects of type of imagery, a third control group that would have permitted a comparison of the treatment to standard medical treatment alone was not incorporated into the design. Without this control group it is impossible to evaluate the possibility that both treatments may have been beneficial compared to pharmaceutical interventions alone. However, the evaluation of changes in spirometry at an individual level indicated that the relaxation imagery was not associated with clinical improvement. Perhaps changes in FEV_1 or FVC for the treatment group may have been statistically significant if compared to a 'no psychological treatment' control group.

Statistical significance was found in only one analysis, post-bronchodilator PEF. This study may be validly criticized because changes in FVC or FEV_1, which are

considered better measures of airway obstruction, were not statistically significant. PEF is more variable and effort dependent than these other measures. However, as discussed in the results section, between-group differences in FVC, FEV_1, and FEF_{25-75} were consistent with the significant treatment * time interaction of post-bronchodilator PEF. Clinical evaluation of individual changes revealed that the majority of the treatment group responded to treatment while none in the referent had a clinically significant response. This strongly suggests that practicing immune modulating imagery improved lung function and relaxation imagery did not. Based on the consistent trends of improvement of lung function, daily PEF, symptoms, and usage of reliever medication, it is likely that statistical significance would have been reached with a larger sample.

While the treatment in this study was designed to modulate inflammatory processes, treatment efficacy was evaluated by measuring lung function with spirometry. The absence of immunological measures, including cytology and cytokine concentration, was an unfortunate but unavoidable limitation of this study. Although lung function improved after practicing asthma specific immune modulating imagery, measures of lung function provide no insight into immunological changes that may have occurred. It is possible that no significant differences in lung function would have been found; yet the treatment might have modulated eosinophil adhesion and other pathological processes in asthma. It has been cautioned in the literature to avoid relying on spirometry when evaluating treatments that effect inflammation rather than bronchoconstriction. Barnes (1998) speculated that pulmonary function tests might have a low sensitivity in the assessment of effects of inhaled corticosteroids. Barnes noted that studies utilizing even 4-fold or greater differences in dose of inhaled corticosteroids may not find statistically significant differences in response. While this is partly due to the dose-response curve of the pharmaceutical, it is also related to fact that spirometry is being used a surrogate measure of decreased inflammation.

The sensitivity of pulmonary function tests to detect treatment effects for anti-inflammatory treatments is limited in patients that have limitations in the amount of improvement in lung function that is possible. Some patients with asthma have irreversible airflow obstruction and do not improve with anti-inflammatory medications.

Other patients may deteriorate while receiving appropriate treatment. Backman, Greenberger, & Patterson (1997) found that despite long term aggressive treatment (6 to15 years) with inhaled corticosteroids and bursts of oral prednisone, 4 out of 8 patients with severe asthma had a yearly decline in FEV_1. Sykes and Cocchetto (1992) asserted that serial pulmonary function testing has limited use in studies on maintenance medications, as non-bronchodilating anti-inflammatory drugs are not expected to produce the acute measurable response that occurs with inhaled bronchodilators. Greater emphasis on serologic tests, bronchoalveolar lavage, provocation challenges, and frequent trough spirometric determinations was recommended to document effective suppression of chronic inflammation.

Even though spirometry is an important method of assessing lung function in a clinical trial, other laboratory measures of airway obstruction could have been used. This was considered when designing the study and airway resistance was measured with a body plethysmograph from the outset. Unfortunately the body plethysmograph assessments were discontinued due to errors in the data. Airway resistance may have been more a sensitive measure of changes in airway obstruction. Residual volume (RV) was not measured in this study. In Zukiwski (1996) one participant with mild asthma had a 17 % decrease in RV, an 11% increase in slow vital capacity. The decreased RV provided additional evidence of decreased small airways obstruction.

Anecdotal reports of treatment benefits were documented in both treatment groups. As well, some participants had large trends of decreased symptoms. It is unfortunate that accepted measures of quality of life were not incorporated into the study, as they would have facilitated statistical comparison of the treatments on this important therapeutic goal.

Was the effect of the treatments evaluated over a long enough period? Trends in diary data indicated trends of improvement in PEF, symptoms, and usage of reliever medication with no notable plateaus. In Zukiwski (1996) diary data continued to improve without a plateau up to the final week of the study. With inhaled corticosteroids it may take as long as 3 months to reach a plateau in response (Barnes, 1998). Lane (1994) noted that complementary treatments should be assessed over an extended time period

and noted as an example that allergen removal studies measure asthma improvement over a course of several months. Improvements in clinical measures did not plateau until 6 months of treatment with inhaled corticosteroids for patients with mild asthma (Juniper, Kline, Vanzieleghem, Ramsdale, O'Bryne, & Hargreave, 1990). Based on trends in diary data in the current study and Zukiwski (1996), it is likely that spirometric measures of lung function would have continued to improve beyond the 8th week of the study. Despite the methodological limitations of the study, it appears that even as a short-term intervention the immune imagery treatment can have a significant impact on pulmonary function and quality of life.

Points of Clinical Interest

Clinical observations in the current study were consistent with those in Zukiwski (1996). The protocol was well received and participants appeared to be motivated and interested in learning the treatment. Elaboration on the education script was required for most participants in the treatment group to understand the desired positive physiological changes and create imagery to represent them. Overall, feedback on the treatment was positive. The current protocol features 7 minutes of passive progressive muscle relaxation induction and 12 minutes of imagery. Once they developed experience with the treatment, some participants expressed impatience with the relaxation induction and wanted to begin the imagery practice while shortening or omitting the relaxation. I repeatedly emphasized the benefits of the induction to encourage adherence to the protocol. In the first study one participant had a conditioned response of falling asleep while relaxing due to historical use of progressive relaxation as a sleep aid. Two others began omitting the induction in the latter half of the study. Spanos, Stenstrom, and Johnson (1988) found that an induction was not necessary for treatment response to suggestions of imagining wart recession and relaxation was not related to wart regression. In contrast, some participants in the current study found the relaxation induction valuable for reducing stress and for improving focus during the imagery component of the treatment. A few participants provided the feedback that the induction should be longer.

It has been reported in the literature that symbolic imagery has been observed to be more effective than concrete imagery (Achterberg et al., 1994). One participant in the

first study had a spontaneous change in their imagery from concrete to symbolic. While I did not study this aspect of the treatment process, my impression during the current study was that concrete or realistic imagery was more 'powerful' for some of the participants. The treatment requires the visual representation of rather complex biological processes. I believe that it is difficult to represent the processes accurately with imagery that is too symbolic.

All participants indicated at the outset of the study that they did believe that the mind has the ability to influence the body to improve health. However I did not enquire if the participants believed they themselves might have the ability to influence their body. The importance of belief became apparent with the experience of participant number 2 in the treatment group. She initially imagined her white blood cells as children playing in a playground. The imagery was very symbolic and did not appear to be a very accurate representation of the desired physiological changes. She practiced the imagery but displayed little enthusiasm during the process. She reported no benefits from the treatment and had no significant changes in diary data. The participant then discovered that she was able to control a headache using imagery and subsequently experienced a cessation of headaches that had occurred on weekly basis. She admitted to me that at the beginning of the study she was confident that others could use their mind to influence their bodies but did not believe that she could do it herself. It appears that once the participant was convinced of the efficacy of imagery in controlling her headaches she demonstrated more progress towards achieving a better response with asthma specific imagery. She developed new asthma imagery that was more realistic and which she felt better represented the desired process. Soon her diary data improved and she began reporting anecdotal benefits. Evaluation of clinical improvement after 8 weeks of treatment revealed a clinically significant response to treatment. For this individual, positive belief in both the treatment and her ability were very important.

Based on my clinical observations, lack of a very strong belief in treatment efficacy does not preclude a significant response to treatment. Some participants were skeptical of the treatment but continued to practice despite feeling discouraged or frustrated over no or only minor changes in symptoms and daily PEF. Their belief in

treatment efficacy and their ability was much lower than observed with newly motivated participant number 2. At the end of the study they were pleasantly surprised by the improvement in their lung function. As seen in the results section, improvements in lung function may not be apparent until bronchodilator medication is withheld and maximal effort is required during spirometric testing.

Overall, my impression is that the treatment protocol is well designed for both research and clinical practice. The induction appears to be beneficial although some do not find it necessary to precede imagery with relaxation after they gain experience with the process. The 20 minute length of practice appeared to be comfortable for the participants and was adequate to accomplish the treatment goals. Although many participants were reluctant to draw their imagery, the drawings were very useful for the therapists to understand the imagery and correct misunderstandings. Some participants had difficulty drawing the imagery and used supplementary written descriptions of the imagery to provide more detail. The education component of the script was adequate for providing an overview of asthma pathophysiology. A more detailed script would be burdensome for both the research participant or patient and the therapist. A therapist with extensive background knowledge and flexibility to answer a variety of questions appears to the best solution.

It is important to encourage the development of new imagery and refinement of existing imagery. Some participants reported that the imagery felt more 'powerful' and effective when the imagery was vivid and had motion. As some individuals gained experience with the imagery, the multiple images appeared to merge into an integrated whole. When practicing each target image, they would pay more attention to that specific component of the whole. Others found that imagining the process from the perspective of being inside their body was very powerful. Although it was not studied, some participants had individual preferences for images they felt were most beneficial. This is one advantage of using imagery that targeted multiple aspects of the disease complex.

Implications for Counselling Psychology

Relaxation therapies have justifiably become a mainstay as a psychological treatment approach to a wide variety of physical health problems. The results of this

study reveal that when appropriate, for example with immunological disorders, a targeted disease specific approach utilizing imagery may be significantly more effective. Finding a significant difference in treatment effect between very similar psychological treatments suggests that treatment choices should me made carefully. More research comparing psychological treatments for physical disease is clearly needed.

Based on clinical experience conducting the two studies, I would like to emphasize the importance of a thorough understanding of asthma pathophysiology on the part of the therapist or researcher. I do not believe that the treatment can be taught to patients or research participants if knowledge about the immune system is limited to that provided in the education script. The education script provides a good overview of asthma pathophysiology targeted with imagery. However, the process of developing meaningful imagery that accurately represents the desired immunological and physiological changes is highly interactive and complicated. The therapist must be able to answer a wide range of questions and correct the many misunderstandings that will occur. For example, I noticed that one participant incorrectly assumed that the eosinophils, which became "sticky" in order to adhere to the blood vessel wall, remained sticky after migrating out of the blood vessel into the tissues of the lung. A more thorough explanation of adhesion, migration, and chemotaxis was provided so the individual's understanding of the process and representative imagery would be more accurate. The research assistants (RA) in this study were provided with education about the inflammatory processes that exceeded the information in the education script. Despite this training, when reviewing case files as part of the supervision process, I recognized errors in the imagery developed by some participants and provided feedback to the RA so they could correct the misunderstanding. Based on this experience I believe it would be unethical to teach a patient to imagine changes in the immune system without sufficient knowledge to correct errors in the imagined process.

Although I have studied asthma pathophysiology extensively, my knowledge remains basic when compared to that of an immunologist. I do not know how detailed the understanding should be to appropriately deliver this treatment without supervision. I can conclude that a psychologist without a strong background in asthma immunology and

medicine would require at minimum many months of intensive study. In order to train the patient in this treatment, the therapist needs to understand not only asthma pathophysiology, but also types and severity of asthma, symptomology, pharmacological treatments, and assessment of lung function. I believe that it would be inappropriate to provide this or any other psychological treatment for asthma without ensuring that the course of the disease is monitored with peak flow and symptom data, and if possible, lung function assessments.

Symptoms are typically the primary outcome measure of treatment efficacy in clinical practice. The results of this study illustrate that patients may have clinically significant benefits from a psychological treatment without concurrent improvements in symptoms. Perhaps symptom improvement may occur more slowly. Alternatively, disease progress may be arrested but symptoms may remain. Thus, whenever possible it may useful to employ objective measures of disease severity. Collaboration with physicians would enable the use of serial measures to evaluate treatment efficacy and progress. Data from well designed single case studies with objective outcome measures would contribute to the body of knowledge on psychological treatments and may stimulate controlled studies on those treatments.

Implications for Medicine

The results of this study have important implications on the practice of allopathic medicine. This treatment should be considered as a viable therapeutic option for asthma that complements current medical practice. Immune modulating imagery was of significant benefit to a wide population of adults with asthma. Adults from both hospital clinics and general practice with atopic, non-atopic, and occupational asthma responded to treatment. Not only were no negative side effects reported, many patients experienced positive side effects such as a newfound sense of control over their disease and reduced stress levels. Decreased dependence on short-acting bronchodilator medications alone is a significant benefit of the treatment. Physicians should become more knowledgeable and open-minded about psychological treatments for physical disease, and consider including them in their repertoire of treatment options. Patients independently seek non-

pharmaceutical treatments and will use them without informing physicians that are non-supportive of these options.

This treatment should be considered a particularly attractive option for physicians treating steroid resistant and steroid dependent asthma. While this study did not evaluate the treatment with these populations, the results clearly support beginning case studies and clinical trials with these populations. This treatment might slow, stop, or even reverse the decline of lung function seen with steroid resistant asthma. Patients with steroid dependent asthma may be able to reduce or eliminate dependence on oral steroids. One patient in the first study was successfully taken off prednisone.

Conventional medicine, despite it's many successes and benefits, is not a panacea for many medical problems. In the case of asthma, pharmaceutical treatments control but do not cure asthma. There are probably many things about asthma that is not yet known or understood with a modern western scientific approach. Perhaps alternative treatments that cure asthma may exist. Acupuncture can be beneficial for a wide range of conditions, yet conventional medicine does not understand why most acupuncture treatments work, and cannot measure the energy meridians it is purported to effect. However, it is encouraging that acupuncture is slowly becoming more accepted by physicians.

Implications for Future Research

The anecdotal findings in Zukiwski (1996) and the clinically and statistically significant results of the current study support further research on the efficacy of immune modulation imagery as an adjunct treatment for asthma. As discussed earlier, the current study should be duplicated with a larger sample. A third control group should be utilized to control for the effectiveness of standard medical treatment alone. Other designs could compare the effect of the treatment on different asthma populations: atopic, non-atopic, occupational asthma, corticosteroid resistant or dependent patients, more severe patients using oral steroids, unstable patients that frequently require emergency treatment or hospitalization, and children or the elderly. Children, having good visualization skills and likely no negative preconceptions about imagery or hypnosis, may be particularly amenable to imagery treatments.

Strategies for improving compliance and decreasing attrition should be employed. For example, paying volunteers an honorarium for completing the study would likely decrease attrition. Computerized peak flow meters or portable spirometers could be employed for daily monitoring of lung function. In addition to measuring PEF and/or FEV_1, these devices record the date and time of measurement. Other laboratory measures of airway obstruction (airway resistance) and bronchial hyperreactivity (methacholine challenge) should be considered. Longer studies may reveal plateaus in the improvement of lung function. Follow-up studies could examine what percentage of patients continue to voluntarily use the treatment after the end of the study.

Future research should compare rates of respiratory infection and colds between treatment and control groups to determine if the immune modulation imagery serves as a protective factor against respiratory illness.

Various immunological measures would be valuable in assessing how the treatment affects the immune system. The treatment targets various components of asthma pathophysiology that could be assessed. Did the treatment modulate mast cell activation and release of histamine and other mediators that are involved in the recruitment and activation of eosinophils? Was there modulation of eosinophil adhesion and activation in the blood and degranulation in the lungs? One of the targets of the treatment was bronchoconstriction. The treatment group was instructed to imagine relaxation of airway smooth muscles without specific instruction as to the mechanisms of bronchoconstriction. Are there changes in pathophysiology not targeted by the treatment such as cholinergic, adrenergic, and other excitatory mechanisms related to bronchoconstriction and airway inflammation? The use of any immunological measures requires the participation of an immunologist with expertise in asthma and a high level of financial support.

While this program of research was stimulated by research on imagery and neutrophil adhesion, the treatment protocol targets several pathophysiological components of asthma. Is the imagery representing modulation of eosinophil activation and adhesion an important component of the treatment? Would the treatment be effective if it were limited to imagery representing decreased eosinophil adhesion?

A training program for therapists should be incorporated into any future studies. This should include standardization of training in imagery treatment processes, clinical skills in delivering relaxation inductions, and asthma pathophysiology. Level of knowledge should be tested and clinical ability in providing the treatment should be evaluated to ensure competence of all therapists. In a larger trial, therapist characteristics such as gender and age could be included in the analysis to examine their effects on treatment outcomes.

Future research may also explore characteristics of the patients that may be related to treatment response. Perhaps those who are more responsive to tests of hypnotizability or have a greater ability to visualize may find the treatment process easier or more effective. The question of whether personality or personal beliefs may have an effect on response to treatment should also be addressed. As well, whether other characteristics of the two treatments examined in this study need to be considered in the design of future studies should also be addressed. For example, physiological indicators of relaxation could be used to evaluate how well relaxation effects were controlled for with the design of the current study.

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APPENDIX A

Patient Information Sheet

Training in Self-Generated Imagery as an Adjunct Treatment for Asthma

This Patient Information Sheet, a copy of which has been given to you, is only part of the process of informed consent. It should give you a basic idea of what the research project is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. The researcher Keith Zukiwski (Education Clinic 492-3746) will answer any additional questions that you have about the research project. Please take the time to read this carefully and to understand any accompanying information.

You have been selected for possible participation in this research study because you have asthma and meet certain requirements about how severe your asthma is and the medications you use.

Objective. The Caritas Research Steering Committee (Edmonton General Hospital, Grey Nuns Hospital, Misericordia Hospital) is funding a research study on the efficacy of a psychological intervention (relaxation and mental imagery) as a supplementary treatment for asthma. Additional support is provided by the Alberta Asthma Centre and the University of Alberta Pulmonary Research Group. This study has been approved by the Research and Ethics Committee of the Department of Educational Psychology (University of Alberta), and the Caritas Research Steering Committee.

Results from a pilot study conducted in 1996 included clinically and statistically significant improvements in lung function, daily measures of peak expiratory flow, and self-reported symptoms. Building on this initial research, the current study is designed to examine the effectiveness of relaxation and imagery as a supplementary treatment for asthma through a more rigorous controlled experiment.

If you participate in this study, you will be trained in a technique that aims at using the mind to help heal the body. You will be taught skills in relaxation and imagery that have been used by doctors, psychologists, nurses and other health professionals for many years. This training is designed to be a treatment for asthma that is used in addition to your current medical treatment. During the study, you will continue taking your medication as instructed by your doctor. The skills you learn can be applied to asthma or other medical problems well after the study is over. This research has the potential to make a significant contribution to the existing research on mind-body healing and psychological treatments for asthma.

Design of Study. The goal of the study is to detect any difference in treatment effect between two kinds of relaxation assisted imagery training. Two treatment groups will be used, each receiving education about asthma, and training in relaxation and imagery. The groups will differ in terms of the kind of imagery they will use. Participants will not be informed about the exact nature of the imagery until they are assigned to a treatment group. It should be emphasized that both groups are treatment groups that will receive training in the use of a potentially powerful psychological treatment. Which treatment you receive will be decided by a method known as "randomization". This means you will be assigned to one of two groups according to a computer-generated code. The chances of receiving one treatment versus the other are almost equal. No one other than the therapist and yourself will know which treatment you are receiving. In the event of an emergency this information would be made available to your physician. At the completion of the study, if one imagery technique is determined to be more effective, then it will be taught to the participants who trained in the other form of imagery. As a result, there is no significant advantage or disadvantage to being assigned to one treatment group over the other.

Voluntary Participation. Your participation in this study is voluntary. You may stop at any time. You may decide to withdraw from the study without affecting your medical care. If you decide to withdraw from the study, you should call the researchers as soon as possible to inform them. The researcher and/or your physician may stop your participation in the study at any time if they decide that it is in your best interest. There are also certain reasons relating to changes in your asthma severity or medications that may also require you to stop participation in the study.

Confidentiality. If you agree to participate, all information provided by you will be kept confidential. It is possible that your medical record at the University of Alberta Hospital, as it relates to this study, will be reviewed for quality control purposes under strict confidentiality by the researchers Keith Zukiwski, Dr. Harissios Vliagoftis, and staff at the pulmonary function lab. You will not be identified by name on any reports or publications resulting from this study. All material and data obtained from this study will be stored and may be used for future analysis and publication without obtaining further consent from you. However, each study arising as a result of information obtained in this study will be submitted for ethics approval.

Expectations. Everyone who takes part in this study must agree to the following expectations of them:

(1). Lung Function:

In order to determine how well this treatment works we have to measure changes in your lung function. You will be involved in the study for two months. This will require you to go to the University of Alberta Hospital two times, once at the beginning of the study and again at the end, eight weeks later. The pulmonary function testing lab is located in the Department of Medicine, 2nd floor, north end of the hospital (room 2E4.23), phone 407-6212. The respiratory therapists will conduct one test which

involves blowing into a spirometer (a computer which has a tube attached to it) as hard as you can. After taking two doses of Ventolin (or other bronchodilator) and waiting 10 minutes, the test will be conducted again. This takes approximately 20 minutes. Before coming in for this test you must stop using certain drugs for a certain number of hours. You must not use beta-2 agonists such as Ventolin for 8 hours, short-acting theophyllines for 12 hours, long-acting theophyllines for 24 hours, or Serevent or Atrovent for 12 hours prior to the test. Please do not use leukotriene inhibitors such as Accolate or Singulair for 3 days prior to the test. Do not consume any caffeine the day of the test. Please record when you last took your medications so you can repeat the process at the end of the study. If you have a smoking history, a second test may be conducted on the first visit to determine how well your lungs pass gases to the blood (diffusing capacity). The first visit will also serve to find out if you meet all the requirements for the study. It is possible you may be stopped from taking part in the study after the first visit.

(2). Asthma Diary & Peak Flow:

You will be provided with an asthma diary on which you will record how often you use your medication, asthma symptoms and severity, and your peak flow rates. If you do not have a Mini-Wright Peak Flow Meter you will be provided with one for the study. Due to the cost of the peak flow meters we request that you return the meter if you withdraw from the study, or when the study is over. It is crucial to have two measurements of peak flow each day, upon waking and at bedtime *before you take your medication.* Each time you measure your peak flow you will blow into the meter three times. You will record the highest of the three blows in your diary. You will be taught how to do this properly.

(3). Training:

You will start the training within a week of the lung function assessment. You will go to the Education Clinic at the University of Alberta once a week for eight weeks (Faculty of Education Clinical Services, Room 1-135 Education North, University of Alberta, ph 492-3746). The researchers will train you in individual sessions. Each visit will be approximately 60 minutes long. Appointments can be made for the day, evenings, and during the day on weekends. You will be given directions how to get there, and coupons for parking or bus rides. You will be taught skills which you will be expected to practice for approximately 20 minutes per day. You will be given a cassette tape that help you to practice. How often you practice will be recorded in the asthma diary.

(4). Drawing:

You will be encouraged to do a small amount of drawing or sketching as part of the training (you can paint if you choose). You are not expected to be good at drawing as the quality is not important. A pad of drawing paper and colored pencils will be provided to you. You will be asked to give your drawings to the researcher at the end of the study.

(5). Follow These Instructions:

- *medication*
  - continue to use medication as directed by your physician
  - do not take drugs such as Aspirin which contain acetylsalicylic acid (ASA) unless approved by your physician (individuals with asthma may have reactions to ASA)
  - refrain from using cold and allergy medications unless you discuss their use with your physician
  - do not use beta-2 agonists such as Ventolin for 8 hours, short-acting theophyllines for 12 hours, long-acting theophyllines for 24 hours, or Serevent or Atrovent for 12 hours prior to the lung function test
  - do not use leukotriene inhibitors (Accolate or Singulair) for 3 days prior to test
  - please record the time you last took your medication so that you can duplicate the process at the end of the study

- *exercise*
  - refrain from beginning an exercise program, or altering a current exercise program for the duration of the study
  - do not exercise within 12 hours before assessment of lung function at the hospital

- *diet*
  - avoid severe changes in how much and what you eat, such as deprivation diets

- *lung function assessment*
  - do not exercise within 12 hours before assessment of lung function at the hospital
  - get a good night's sleep the night prior to assessment of lung function at the hospital
  - do not use beta-2 agonists such as Ventolin for 8 hours, short-acting theophyllines for 12 hours, long-acting theophyllines for 24 hours, or Serevent or Atrovent for 12 hours prior to the lung function test
  - do not tell the respiratory therapists which type of training you are receiving
  - bring your peak flow meter for each appointment at the hospital for lung function assessment
  - do not use leukotriene inhibitors (Accolate or Singulair) for 3 days prior to test
  - please record the time you last took your medication so that you can duplicate the process at the end of the study
  - do not consume any caffeine the day of the test

- *asthma diary and peak flow*
  - on a daily basis record asthma symptoms, medication usage, and home practice of the treatment you have been taught
  - record the highest of 3 blows into your peak flow meter, 2 times daily: upon

waking and at bedtime before you take your medication
- try to measure your peak flow at approximately the same time each day (± 30 minutes)

- *training and practice*
  - practice the treatment at least once each day for approximately 20 minutes
  - do not discuss the training you receive with other asthma patients as they may be involved in the study

- *inform researcher in the event of*
  - use of oral corticosteroids (in pill form)
  - sickness or infection (including colds)
  - changes in prescription or non-prescription medications
  - sleep disturbances
  - pregnancy
  - surgery
  - severe psychological stressors
  - severe weight changes

If you decide not to participate in this study yet want to be trained in techniques that use the mind to help heal the body, the researcher can refer you to a psychologist who will teach you these methods on a fee for service basis.

If you desire help, either to continue treatment after the study is completed, or to deal with any issues that may arise during treatment, you will be given an appropriate referral.

APPENDIX B

Consent for Patients

Training in Self-Generated Imagery as an Adjunct Treatment for Asthma

I acknowledge that the research project described in the preceding information sheet has been explained to me and that any pertinent questions I have asked have been answered to my satisfaction. I have been informed of the alternates to participation in this study and all the known risks and discomforts.

I understand that Keith Zukiwski or Dr. Redwan Moqbel will answer any additional questions that I have about the research project. Should I decide to withdraw from the study at any time, I may do so without prejudice to my overall care.

I understand that I will receive a copy of the information sheets and this signed consent form, and that this project may be reported, but I will not be identified. I have been assured that my confidentiality will be respected. I consent to participate in this study.

Name of Participant (please print)	Signature of Participant
Name of Witness (please print)	Signature of Witness
Name of Investigator (please print)	Signature of Investigator
Date	

APPENDIX C

Asthma Diary

Diary of participant #8 (treatment group) provided as example of asthma diary.

ASTHMA DIARY Tu DATES: Sept 10 to Oct 10 NAME: ______

Section	Row	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	DATE Sept 8	Th 10	F 11	S 12	S 13	M 14	Tu 15	W 16	Th 17	F 18	S 19	Su 20	M 21	T 22	W 23	Th 24	F 25
PEAK FLOW	COLUMN	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Enter best of 3 blows. At the same time each day (+ or - 30 minutes) if possible.	Upon waking in A. M. Typical time: 7:30	490	450	480	460	450	470	460	470	480	470	470	480	570	520	500	520
If you miss a reading please mark it "ND" (not done).	Bedtime. Typical time: 12:00 AM	550	560	540	550	540	[illegible]	520	530	540	540	530	550	560	530	540	540
MEDICATIONS	Name of Medication and Dosage																
Record the number	SEREVENT	2x2	2x2	2x2	"	"	"	"	4	4	4	4	4	4	4	4	4
of times prescription	PULMICORT	2x2	3x2	2x2	"	"	"	"	4	4	4	4	4	4	4	4	4
and non-prescription	RHINOCORT	2x1	2x1	2x1	"	"	"	"	4	4	4	4	4	4	4	4	4
medication was	VENTOLIN	-	-	1	-	1	1	1	1	1	1	1	1	1	2	1	1
used per day	ZOLOFT 50mg															1	-
SYMPTOM SEVERITY																	
Rate each symptom category:	Wheeze	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
0 = No symptoms	Dry Cough	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1 = Mild	Cough with expectoration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2 = Moderate	Shortness of breath	1	2	2	2	2	2	2	2	1	1	1	1	1	1	2	2
3 = Severe	Chest tightness or discomfort	1	1	1	2	2	2	2	2	1	1	1	1	0	0	1	0
4 = Very Severe	Night or early morning waking due to asthma	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
5 = Required medical attention	Had to take a rest	2	2	1	2	3	2	2	2	2	2	2	2	1	1	1	2
(Please use whole numbers only)	Sensitivity to odors & *inhaled irritants*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HOME PRACTICE																	
Enter the number of times you practiced	Practice with audio tape (required)	ND	ND	ND	ND	ND	ND	1	1	ND	ND	1	1	1	1	1	1
	Practice without audio tape (optional)															1	
	COLUMN	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

Section	Row	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
	DATE Sept 8	Sa 26	Su 27	M 28	Tu 29	W 30	Oct 1	F 2	SA 3	Su 4	M 5	T 6	W 7	Th 8	F 9	Sa 10
PEAK FLOW	COLUMN	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Enter best of 3 blows. At the same time each day (+ or - 30 minutes) if possible.	Upon waking in A. M. Typical time: 7:30	520	500	530	480	500	510	510	500	510	500	500	520	500	480	530
If you miss a reading please mark it "ND" (not done).	Bedtime. Typical time: 12:00 AM	510	510	530	510	540	500	510	500	560	480	470	480	470	480	500
MEDICATIONS	Name of Medication and Dosage															
Record the number	SEREVENT	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
of times prescription	PULMICORT	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
and non-prescription	RHINOCORT	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
medication was	VENTOLIN	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
used per day	ZOLOFT 50mg	-	1	1	-	1	1	1	1	1	1	1	1	1	1	1
SYMPTOM SEVERITY																
Rate each symptom category:	Wheeze	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1
0 = No symptoms	Dry Cough	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1 = Mild	Cough with expectoration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2 = Moderate	Shortness of breath	2	2	2	2	2	1	2	1	1	1	1	1	1	1	1
3 = Severe	Chest tightness or discomfort	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1
4 = Very Severe	Night or early morning waking due to asthma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5 = Required medical attention	Had to take a rest	2	2	2	2	3	2	2	2	3	2	2	2	2	3	3
(Please use whole numbers only)	Sensitivity to odors & *inhaled irritants*	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
HOME PRACTICE																
Enter the number of times you practiced	Practice with audio tape (required)	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
	Practice without audio tape (optional)															
	COLUMN	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

ASTHMA DIARY

DATES: Oct 11/98 to _____ NAME: _____

	DATE Oct/98	Su 11	M 12	T 13	W 14	Th 15	F 16	S 17	Su 18	M 19	T 20	W 21	Th 22	F 23	S 24	Su 25	M 26	Tu 27	W 28	Th 29	F 30	Sa 31	Su 1	M 2	Th 3							
PEAK FLOW	COLUMN	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Enter best of 3 blows. At the same time each day (+ or - 30 minutes) if possible. *If you miss a reading please mark it "ND" (not done).*	Upon waking in A. M. Typical time: 9:30 AM	540	490	530	530	520	530	510	510	520	530	520	510	530	550	500	530	500	520	510	500	490	510	530	530							
	Bedtime. Typical time: 12:30 AM	550	500	530	530	500	480	500	520	550	520	530	480	530	550	515	500	500	510	520	530	510	520	530								
MEDICATIONS	Name of Medication and Dosage																															
Record the number of times prescription and non-prescription medication was used per day	SEREVENT	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4							
	PULMICORT	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4							
	RHINOCORT	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4							
	VENTOLIN	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							
	ZOLOFT 50mg	1	1	1	1	1	N/A	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1							
SYMPTOM SEVERITY																																
Rate each symptom category: 0 = No symptoms 1 = Mild 2 = Moderate 3 = Severe 4 = Very Severe 5 = Required medical attention (Please use whole numbers only)	Wheeze	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1							
	Dry Cough	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							
	Cough with expectoration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							
	Shortness of breath	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1							
	Chest tightness or discomfort	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1							
	Night or early morning waking due to asthma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							
	Had to take a rest	2	2	2	2	2	2	2	2	3	2	3	2	2	2	2	3	2	2	3	3	3	2	2	2							
	Sensitivity to odors & inhaled irritants	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							
HOME PRACTICE																																
Enter the number of times you practiced	Practice with audio tape (required)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1							
	Practice without audio tape (optional)																															
	COLUMN	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

APPENDIX D

Introduction and Orientation: Treatment A & B

Introduction
(Initial greeting, thank for participating, and general conversation to establish rapport)
Consent
Sign consent form.
Questions

How long have you had asthma? How has it effected your life? How have you controlled your asthma? Have you tried to use you mind to control your asthma in any way? Do you believe it is possible for the mind to influence the body? Why? What are the positive consequences of controlling your asthma? What are the negative consequences of controlling your asthma? Address any stated reservations.

Read Modified Version of Hall's (1990) Pre-Treatment Script

(Script is intended to allay misconceptions or fears, emphasize "allowing" the experience to happen rather than "trying", elicit modality preferences, elicit calm imagery, and prepare for the upcoming experience).

Homework Instructions: Orientation (Presented orally and provided as a handout.)

At home, take several minutes to relax your body from feet to head, think of your calm and relaxed place or time. Most people like to do this with their eyes closed.

When you think of the asthma that you currently have, what image, or images, come(s) to your mind. The image that develops can include pictures, sounds, smells, tastes, and/or feelings. Take your time, and be receptive to any images that may come into your awareness from your unconscious. Your personal representation of asthma does not need to conform to any drawings or pictures you have seen before. Be creative. Throughout the week, be alert to any images that may come to you when awake or even in your dreams.

Make a drawing, or drawings, of the image as best you can. You will not be evaluated on your artistic ability.

I will provide you with paper and colored pencils. If you wish, you can also write down a description of your experience. Please feel free to use paint or use other art mediums, although it is preferable if you use color.

Go through the same process to develop, then draw, an image of the medication you are currently taking for asthma.

Please bring your drawings to the next session.

APPENDIX E

Asthma Education Script: Treatment A & B

Education Script and Generation of Imagery

(All participants are encouraged to ask questions to ensure they understand the information presented. A copy of this education script is provided during the session (with protocol instructions removed).

Even though you may know some things about asthma, I would like to review some important information with you. When you breathe in, the air travels through the nose and mouth, and down your trachea (indicate trachea on self), which is commonly known as your windpipe. At the top of the lungs the trachea subdivides into two bronchial tubes, one going to the left lung, the other going to the right lung. The bronchial tubes then subdivide many times into increasingly smaller tubes that have tiny air sacs on the ends where oxygen exchange occurs.

In asthma, the immune system which protects us from bacteria, viruses, and parasites, is over-active. Some of the cells of the immune system, which are meant to protect us from noxious materials, are produced in greater numbers and then gather in the lungs. There they act as if they are protecting the body when there is in fact little if any threat. Their activation cause inflammation of the airways and this in turn results in contraction or spasms of the muscles that surround the airways which make it more difficult to breath.

Image 1: Blocking the allergen-antibody complex which functions as an initial trigger for the release of mediators and proteins. Are you allergic to anything? Allergies are often involved in causing this inflammation. Allergies occur when your immune systems reacts to a foreign substance, such as (insert relevant allergen), that is not usually harmful to the body. These substances are called allergens. The immune system has developed a way of recognizing that the allergen is present, and alerting its cells to take action. The alarm system consists of a molecule called an antibody that recognizes only that one type of foreign substance. There is a class of sticky antibodies that are found tightly bound to the surface of certain immune system cells called mast cells, which are in the tissues of the nose, mouth, and lungs. When the allergen enters the body, the antibody that recognizes it will latch onto it, inducing the cell to release many substances such as histamine and others which cause symptoms like itchy and watery eyes and tightening of the muscles around the airways. These cells also release molecules which alert other cells of the immune system in order to recruit more of them to the site of inflammation and to activate them to release more of their stored chemicals.

(Immune imagery questions (omit for Group B): How would you imagine, in any way that is meaningful for you, your immune system correcting its mistake and no longer recognizing (insert relevant allergens) as harmful? With the mast cells in the tissues of the lungs, remaining calm and quiet, saving their special chemicals for when they are really needed?)

Image 2: blocking infiltration and recruitment of immune and inflammatory cells such as T-cells and eosinophils through a decrease in their activation and adhesive capacity, and blocking infiltration of immune and inflammatory cells such as T-cells and eosinophils through a decrease in the activation of endothelial cells. As mentioned before, the mast cells release messengers that tell other cells of the immune system, which are circulating in the blood, to come to that same location and help. There are a number of different kinds of immune cells that behave in a similar way, we shall refer to them all as white blood cells.

When they are calm, these WBC's travel around the body with the rapid flow of blood just waiting to be called into action. When they receive the recruitment messages, these white blood cells become alert, active, and excited. When they become excited, the WBC's change a number of important proteins that are on the surface of the cell, so they can act like antenna. The cells also send extra molecules of protein from the inside of the cell to its surface to make it even more sticky. The sticky WBC's can then grab on to the wall of the blood vessel, slow down, and begin rolling along the wall of the blood vessel. The walls of the blood vessels in the area where the WBC's have been summoned to, become coated with molecules that are designed to connect with the molecules that have appeared on the surface of the white blood cells. This lets the WBC's know where to stop rolling, and then squeeze through the gaps in the wall of the blood vessel, into the area of tissue they were summoned to. Thus both the walls of the blood vessels and the white blood cells have become sticky.

With asthma, the immune system is over active. It would be desirable if the WBC's ignored the signal to become excited, and if the WBC's and the blood vessels became less sticky. Researchers have already proven that you can make WBC's more or less sticky just by imagining the change you want. This is what we want to do now. (Immune imagery questions (omit for Group B). How would you imagine your white blood cells and blood vessels becoming less sticky? Can you incorporate the desirable change of the WBC's ignoring the signals?)

Image 3: Blocking the release of eosinophil-derived cytotoxic proteins through a decrease in inflammatory cell activation. After the white blood cells stick to the wall of the blood vessel, they squeeze through the wall and move into the tissues of the lung (and nose?) where they release toxic substances that damage the healthy tissues of the lungs.

(Immune imagery questions (omit for Group B): How would you imagine both the white blood cells that traveled to the tissues of the lungs, and the ones that are normally there, remaining calm and quiet, saving their special protective chemicals for when they are really needed?)

Image 4: Relaxation of Smooth Muscle. Narrowing of the airways is partly caused by the tightening of the muscles in the walls of the trachea and bronchial tubes. These muscles can spasm and tighten, reducing the size of the airway. (Immune imagery questions (omit for Group B). How would you imagine the muscles in the walls of the trachea and bronchial tubes becoming relaxed and loose?)

Image 5: Reduction in the production of mucus. Increased removal of mucus that is present, through thinning of the mucus, ciliary action, and efficient coughing.

The airways may become blocked by increases in the amount of mucus. Mucus is produced by small glands that line the airways. The mucus may become thick making it

harder to remove by coughing and the sweeping action of the little hairs in the airway called cilia. (Immune imagery questions (omit for Group B). How would you imagine the glands producing less mucus? How would you imagine the mucus becoming thinner, being swept up and out of the lungs by the cilia, and expectorated by coughing.)

Image 6: End state imagery. I would like you also to develop an image that represents the final healed state with healthy, clear, and open airways. (Immune imagery questions (omit for Group B). How would you imagine your airways healthy, with clear and open paths?)

Calm scene imagery (Group B only). Now, I'd like you to imagine that you are somewhere where you feel very calm and relaxed--totally free of tension and care. Most people find this easier with their eyes closed, but you may leave them open if you so desire. In this place where you are calm and relaxed, you should be by yourself--without the distraction of other people--and you shouldn't imagine doing anything in this scene except relaxing and enjoying it. Maybe you imagine yourself on a beach or in the mountains. We'll be calling this your calm scene, and we'll be using it to help you relax. Tell me about your scene--what it is like-- in as much detail as you can imagine. (Three distinct calm scene images are developed.)

Homework Instructions: Group A (Presented orally and provided as a handout)

1) Draw the imagery developed in this session . You only need to draw a given image once, not every session.

(a). How would you imagine, in any way that is meaningful for you, your immune system correcting its mistake and no longer recognizing the things you are allergic to as harmful? With the mast cells in the tissues of the lungs, remaining calm and quiet, saving their special chemicals for when they are really needed?

(b). How would you imagine your blood vessels and white blood cells becoming less sticky?

(c). How would you imagine both the white blood cells that traveled to the tissues of the lungs, and the ones that are normally there, remaining calm and quiet, saving their special chemicals for when they are really needed?

(d). How would you imagine the muscles in the walls of the trachea and bronchial tubes becoming relaxed and loose?

(e). How would you imagine the glands producing less mucus?

How would you imagine the mucus becoming thinner, being swept up and out of the lungs by the cilia, and expectorated by coughing.

(f). I would like you also to develop an image that represents the final healed state with healthy, clear, and open airways.

2) Please listen to tape once a day.

3) Some people find it beneficial to practice the imagery for brief periods during the day, especially when you feel some symptoms and when you take your medication.

Homework Instructions: Group B (Presented orally and provided as a handout)

1) Draw the imagery developed in this session if you have not already done so. You only need to draw a given image once, not every session.

2) Please listen to tape once a day.

3) Some people find it beneficial to practice the imagery for brief periods during the day, especially when you feel some symptoms and when you take your medication.

APPENDIX F

Treatment A: Immune Modulation Imagery

Read induction script (Hall, 1990, modified to decrease length)

(The 7 minute induction incorporates relaxation, suggestions, and elicitation of classic hypnotic phenomena and "is geared toward creating a psychological ritual that everyone can experience" (Hall, p. 215).

Treatment Imagery

(Pause for approximately 1 min following each image).

Image 1. Now I would like you to begin allowing yourself to imagine--in any way that is meaningful for you--your immune system correcting its mistake--and no longer recognizing as harmful--the things you are allergic to--the mast cells in the tissues of the lungs--remaining calm and quiet--they can now save their special chemicals for when they are really needed--fully expecting this to happen--fully expecting that this is happening now--it is possible you may see, feel, hear--taste, and even smell this happening--what ever way is right for you--use the next moments of silence to imagine as fully as possible, your immune system no longer recognizing as harmful, the things you were allergic to--imagining your mast cells--calm and quiet--for the next minute until you hear my voice again.

Image 2. And now, allow yourself to imagine--as fully as possible--your white blood cells becoming less sticky--and your blood vessels becoming less sticky--however you will imagine this--whatever colors, sounds, feelings there may be--fully expecting it will happen--white blood cells--less sticky--blood vessels--less sticky.

Image 3. Imagine all the white blood cells--in the tissues of the lung--becoming calm and quiet--saving their special chemicals--for when they are really needed. They really don't need to be as active as they have been--becoming calm and quiet. Making the image as powerful as you can. You may see the imagery, and hear any sounds that might be there, and feel it happening.

Image 4. Now, imagine the muscles in the walls of the trachea and bronchial tubes becoming relaxed and loose--muscles becoming relaxed and loose--the airways opening up as they become relaxed and loose. You may notice a change in how they look--how it sounds--and it may even feel differently as the muscles become relaxed and loose.

Image 5. Imagine the mucus glands which line your airways--producing less mucus--thin mucus--and as the mucus in your lungs becomes thinner, it is swept up and out of the lungs by the cilia where it can be removed when necessary by a cough--mucus glands producing less mucus--thin mucus--the mucus becoming thinner and being swept upwards.

Image 6. And you can now imagine your lungs as healthy, with clear, and open airways. Imagine what that looks like, feels like, sounds like. Healthy, clear, and open airways.

Image integration. And now, possibly in a creative and interesting way, allow yourself to combine some or all of these healing images--in any way that is meaningful for you--or you can imagine whatever may be most beneficial for you at this time--go ahead and do that now.

Reorient. And now you can use the next few moments to slowly begin becoming more alert and aware of your surroundings as you conclude this healing session--take your time and go at your own pace--(10 sec)--if you are ready, you can now open your eyes if you have not already done so--feeling awake and refreshed. Take a moment to recall this experience. Draw any changes in your imagery or new imagery that may have developed. Write down any insights or revelations you may have had.

Discuss and validate experience. How do you feel? What was that experience like for you? Was that what you expected? Were you deeply relaxed? Where was your attention focused? Could you describe what you imagined? Did you always hear my voice? Did you experience any discomfort? Do you have any questions? Is there anything that you can do to make the imagery more powerful? Why don't you try that now and see what happens? What were you aware of in your body? What are you aware of now?

Assign home practice. Please listen to tape once a day. Some people find it beneficial to practice the imagery for brief periods during the day, especially when you feel some symptoms and when you take your medication. Provide audiotape handout.

APPENDIX G

Treatment B: Calm Scene

Read induction script (Hall, 1990, modified to decrease length)

(The 7 minute induction incorporates relaxation, suggestions, and elicitation of classic hypnotic phenomena and "is geared toward creating a psychological ritual that everyone can experience" (Hall, p. 215).

Image 1. And I'd like you to begin allowing your calm scene to develop--as fully as you can--a time, a place--that you feel comfortable and relaxed. You may notice that it is the same as before--or it may have changed in certain ways. And that's just fine. All that is really important--is that you just allow it to happen--and as you begin to notice certain details--of your experience--you may enjoy a growing sense--of comfort--and relaxation. Use the next minute or so of silence--to imagine it as fully as possible--until you hear my voice again (60 sec silence).

And now as you stay with the same image, I wonder if you will enjoy--how naturally you may become aware--of certain sights--sounds--sensations--and you may also imagine smells and tastes--and emotions that you would feel--you may feel peace--serenity--calmness--there may be other feelings you are aware of. I really don't know. Continue to stay with that image. (60 sec silence).

Image 2. And now, begin allowing another calm scene to develop--as fully as you can--a time, a place--that you feel comfortable and relaxed. Just allow it to happen--what ever way is best for you (60 sec silence).

Staying with that image, allow your attention to focus on certain details of your experience--allow that image to become as powerful as possible--feeling calm and relaxed--staying with that image, until you hear my voice again, in the next minute or so (60 sec).

Image 3. And now I'd like you to begin allowing your final calm scene to develop--as fully as you can--a time, a place--that you feel comfortable and relaxed. Just allow it to happen. You may enjoy a sense--of comfort--and relaxation. Use the next moments of silence to imagine it as fully as possible (60 sec silence).

Feeling relaxed--and calm--that's right. Aware of the sights--sounds--sensations--smells--and tastes--and emotions. Allow that image to become as powerful as possible (60 sec silence).

Image integration. And now, possibly in a creative and interesting way, allow yourself to combine some or all of these healing images--in any way that is meaningful for you--or you can imagine the calm scene image that is most beneficial for you at this time--go ahead and do that now (60 sec silence).

Reorient. And now you can use the next few moments to slowly begin becoming more alert and aware of your surroundings as you conclude this healing session--take your time and go at your own pace--(10 sec)--if you are ready, you can now open your eyes if you have not already done so--feeling awake and refreshed. Take a moment to recall this experience. Draw any changes in your imagery or new imagery that may have developed. Write down any insights or revelations you may have had.

Discuss and validate experience. How do you feel? What was that experience like for you? Was that what you expected? Were you deeply relaxed? Where was your attention focused? Could you describe what you imagined? Did you always hear my voice? Did you experience any discomfort? Do you have any questions? Is there anything that you can do to make the imagery more powerful? Why don't you try that now and see what happens? What were you aware of in your body? What are you aware of now?

Assign home practice. Please listen to tape once a day. Some people find it beneficial to practice the imagery for brief periods during the day, especially when you feel some symptoms and when you take your medication. Provide audiotape handout.