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BEHAVIORAL RISK FACTORS OF NEAR-FATAL ASTHMA:
A DOUBLE BLIND, CASE-CONTROL STUDY

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAI'I IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PUBLIC HEALTH
MAY 1996

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St. Francis Medical Center - West
The Queen's Medical Center
Wahiawa General Hospital

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I am grateful to numerous severe asthmatics and pulmonary physicians for their cooperation with this project. To Yoko Shimoyoshi, Rani Sanderson, Amy Sanderson, Frank Rincon and Gina Hikiji, I am most grateful for their support and patience during this study period.
ABSTRACT

Problem statement. Asthma mortality is excessive and may be reducible. Behavioral risk factors for asthma death are difficult to identify, and are often too nonspecific to be of predictive value.

Methods. A case-control study of 19 cases with near-fatal asthma who were matched for gender, age, asthma treatment and severity to 19 controls was used to examine behavioral, historical and symptomatic risk factors of near-fatal asthma. Subjects were a sample of all non-military, near-fatal asthma cases on the Island of Oahu, Hawaii. Age limits were 18 - 46 years. A professional interviewer administered three previously validated questionnaires, respiratory disease symptoms and history, psychological symptoms and social support. Both the interviewer and subjects were blinded to the subject's status as case or control.

Results. Major findings include severe asthmatic controls under medicating compared to near-fatal asthma cases, and that they were otherwise very similar. As a study group the subjects (cases and controls) were more often low income, psychologically distressed, female and of Hawaiian ethnicity who are seeing a physician pulmonary specialist and being prescribed appropriate medications. Medication compliance was poor. Sixty percent of the subjects had at least one parent
with asthma. Mean duration of asthma was 21.5 years. There was a very high (>16%) mortality rate among potential near-fatal asthma subjects.

Discussion. These data suggest that restraint in anti-asthma medication use may protect severe asthma patients from near-fatal attacks. These data confirm the similarity of subjects with near-fatal asthma and severe asthma.
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PROBLEM STATEMENT

The prevalence of bronchial asthma is increasing in the industrialized nations of the world. In the U.S. asthma prevalence has increased seventy-one percent (71%) from 1970 to 1990 (American Lung Association, Lung Disease Data 1993). There were 7 - 20 million asthmatics in the U.S.A. in 1987 (Evans et al, 1987). Concomitantly asthma mortality is rising in the face of or perhaps because of increased understanding of the pathophysiology and diagnosis of asthma, as well as, the presence of new, more effective drugs for asthma treatment. Asthma mortality accounted for 4869 deaths in 1989, an increase of seventy-two percent (72%) since 1980 (Workshop on Environmental and Occupational Asthma, 1990; American Lung Association, Lung Disease Data 1993). From 1982 through 1991 the annual age-adjusted death rate for asthma increased 42%, from 3.4 per 1 million population to 4.9 per 1 million (Massachusetts Medical Society, 1995). Asthma included with bronchitis and emphysema was the fifth leading cause of death in the 15 - 24 year old population of Hawaii in 1988 (Department of Health, State of Hawaii, 1988). In 1979 ICD-9 codes replaced the 8th revision of the codes. This revision effected asthma prevalence rates as asthmatic bronchitis was reclassified from bronchitis to asthma (Weiss and Wagener, 1990); however, the data from 1982 - 1991 is well beyond those revisions. During recent decades there has been no change in the definition of asthma, or improvement in
diagnosis that might affect reporting. Further, there is no reason to believe that asthma complaints would be increased artificially as there has been no change in incentive or popularity of the disease. These reports show a significant increase in asthma mortality that was not expected; thereby, justifying the use of the term epidemic (Morton, Hebel, McCarter, 1989).

Hospitalizations for asthma are increasing in the U.S. as are health care costs (National Center for Health Statistics, 1986). The hospitalization rate for asthma increased twenty-two percent (22%) from 1979 - 1990 (American Lung Association, Lung Disease Data 1993). Asthma was the primary diagnosis for 454,000 hospital discharges in 1988. Hospitalization for asthma was higher for females than males and non-white hospitalizations were twice that for whites. Non-whites also had twice as much asthma mortality as whites (Weiss and Wagener, 1990).

Asthma is the reason for 6.5 million doctor's office calls, 1.8 million emergency room visits, 0.5 million hospital admissions, and 1.0 million workdays lost per year (Workshop on Environmental and Occupational Asthma, 1990). Health care expenditures for asthma are estimated to have exceeded $4 billion in 1988 (NHLBI, Executive Summary, 1991).
"In the United States, analysis of the 1978 Social Security Disability Survey showed that 7.7% of respondents identified asthma as a personal medical condition, and 1.2% (15% of all those identifying with asthma) attributed it to workplace exposure" (Blanc, 1987). Occupational asthma is becoming of great concern as increasing numbers of sufferers are coming to businesses and government looking for permanent disability compensation. Scores of substances have been implicated in the etiology of occupational asthma (Chan-Yeung, 1990).

Statistics for Hawaii reflect National trends with the following differences. There is a disproportionately high prevalence of asthma among Hawaiian/Part Hawaiians and the residents of the islands of Kauai, Hawaii and Windward and Waianae coasts of Oahu. The Department of Health, School Health Branch ranked asthma as the most prevalent chronic condition reported in public schools in 1991-1992 (American Lung Association of Hawaii, Lung Disease Statistics 1993).

This asthma epidemic and unexpected increases in mortality are surprising as most asthma specialists feel that well managed patients should not die of asthma (British Thoracic Association, 1982; Nguyen, Patterson, Sly, 1990; Sly, 1984). As a result the National Institutes of Health and U.S. Public Health Service through the National Heart, Lung and Blood Institute convened an Expert Panel on the Management of
Asthma. This panel developed a National Asthma Education Program with focus on primary, secondary and tertiary prevention of asthma as the concept basic to the treatment of acute and chronic asthma (NHLBI, 1991). The medical community responded calling for research directed at all levels of asthma prevention (Bailey, Clark, Gotsch, Lemen, O’Conner, Rosenstock, 1992).

This dissertation presents the results of such research with focus on the tertiary prevention of bronchial asthma. This research points to causal factors in the precipitation of near-fatal asthma attacks and generates knowledge that may aid in the prevention of premature deaths from bronchial asthma by providing useful new information for the prevention activities called for by NHLBI. This research examines behavioral factors adds support to some emerging ideas that asthma death is more than a problem of biochemistry, immunology and medical treatment; it is a very complex issue of human physiology, psychology and sociology.

The definition of asthma established by the National Heart Lung and Blood Institute expert panel (NHLBI, 1991) will be used to guide this research.
"Asthma is a lung disease with the following characteristics:
1. Airway obstruction (or airway narrowing) that is reversible (but not completely so in some patients) either spontaneously or with treatment.
2. Airway inflammation
3. Airway hyperresponsiveness to a variety of stimuli"

As a working definition for this study near-fatal asthma attack is defined as follows:

An acute asthma exacerbation that has resulted in endotracheal intubation and placement of the asthmatic on continuous artificial mechanical ventilation. This definition implies the necessity of hospital admission to the intensive care unit.
THEORETICAL FRAMEWORK

In order to prevent asthma fatalities etiologic factors contributing to risk must be identified. The very specific factors associated with the risk and mediation of asthma number in the thousands. Most, if not all, are to some degree interdependent variables. It is not well known which of the etiological factors of asthma may be major factors contributing to asthma mortality. A brief, general outline of potential asthma risk factors follows:

Genetic factors - a multiplicity of genetic factors have been associated with asthma; although no specific allele has been identified (Burney, 1993). Genetic factors have not been directly linked to asthma mortality.

Physiologic factors - twenty to thirty specific biochemicals produced by the human body are linked to asthma involving complex relationships between intracellular processes, cell membrane chemistry, neurohormones, immune and inflammatory response, and physiologic psychology.

Environmental factors - referring to the physical environment hundreds of substances have been identified as precipitating asthma attacks. No single antigen has been found responsible for asthma death.
Psychological factors - numerous psychological conditions are associated with asthma mortality; however, it is difficult to determine temporal relationships. Psychological factors have been examined in near-fatal asthmatics in only one case-control study (Boulet, Deschesnes, Turcotte, and Gignac, 1991).

Coping skills - asthma is sometimes defined as hypersensitivity to the external and internal environment. Asthmatics vary greatly in the ways they personally cope with their hypersensitivities.

Social support - asthmatics with poor social support often have trouble with asthma control and access to health care.

Knowledge level - common sense would dictate that asthmatics who understand their disease and its treatment will have better controlled asthma. In spite of this healthcare providers, even asthma specialists, have died of asthma.

Medical care - there is wide variation in access to health care and quality and quantity of health care available.

The study of risk factors of asthma mortality is complicated by the fact that the subjects are deceased and that the facts immediately prior to their death are difficult to determine;
however, many studies have been done. The determination of etiologic factors for sudden death from asthma has taken many forms from largely anecdotal accounts, to case reports of death (Rao, Polos, Walther, 1990; Niggeman and Wahn, 1992), to identification of groups with unusual incidence of asthma deaths (Fletcher, Ibrahim, and Speight, 1990; Jackson, Sears, Beaglehole and Rea, 1988; Pauloazzi, Coleman, and Buist, 1986). These descriptive studies have not been able to establish causal relationships between risk factors and asthma death. Additional descriptive studies have investigated associations between suspected risk factors and those persons who have died of asthma (Benotar, 1986; Sears and Rea, 1987; Stableforth, 1983; Walker, Greenberger and Patterson, 1990). Unfortunately without control groups these studies cannot rule out multiple confounding variables. Since asthma death is a relatively rare and unpredictable event, prospective cohort studies have not been able to establish absolute risk.

Case-control studies have been published on patients who died from asthma (Crane et al, 1989; Grainger et al 1991; Rea et al 1986; Spitzer et al, 1992; Strunk, Mrazek, Furmann, LeBrecque, 1985).
Assessment of risk factors by studying the deceased was of necessity limited to hospital records.

It has been suggested (Beasley, Pearce and Crane, 1991) "that fatal and near fatal attacks of asthma may have common causes, and that studying non-fatal asthma attacks (as well as being of value in itself) may provide useful information on the factors associated with fatal asthma attacks." Some of the advantages of case-control studies of near-fatal asthmatics are that the time trends and facts prior to the attack can be better determined, the case and the control can be interviewed, information may be obtained from hospital records in a similar manner, and the case and control can be involved in physiological studies. A case-control study using asthmatics who experienced near-fatal attacks as cases and asthmatics with similar severity of disease who have not had near-fatal attacks as controls would permit a more in-depth comparison of factors other than hospital records such as behavioral and attitudinal variables like medication compliance, social support, and psychological factors.

This case-control study is an observational study rather than experimental and by definition, retrospective. Like most
case-control studies it identifies effects, near-fatal asthma attacks, and seeks to understand the causes. As such this is exploratory, analytical research (Schlesselman, 1982).

This research project addresses the following variables:

Controlled variables - Age (+-5yrs), gender, asthma severity (asthma discharge medications, previous asthma hospital admission), absence of COPD, quality of medical care (primary pulmonary physician, medical center), and time of index asthma exacerbation

Outcome variable - Near-fatal asthma

Causation variables - Medication compliance, psychological symptoms, social support, level of education, household income, marital status, ethnicity, parental asthma, age of asthma onset, wheeze, dyspnea, cough, phlegm production, hayfever, pneumonia, cigarette smoking and dusty occupation
REVIEW OF THE LITERATURE

Previously researchers have investigated factors contributing to the death of patients with fatal asthma attacks (Sears and Rea, 1987; Stableforth, 1983, Benotar, 1986; Walker et al, 1990). These studies and others have identified scores of potential factors contributing to death from asthma (see Table 1). Other factors have been shown not to contribute (see Table 2). These studies offer no evidence that asthmatics of similar severity but who survive such attacks do not have the same contributing factors as those who died.

Recently several case-control studies have been conducted matching cases, those who died of asthma, to living asthmatic controls (Strunk, et al, 1985; Rea, Scragg, Jackson, Beaglehole, Fenwick and Sutherland, 1986; Crane, et al, 1989; Pearce, et al, 1990; Grainger, et al, 1991 and Spitzer, et al, 1992). In one of these studies Rea et al, 1986 matched 44 adult cases to one control group of hospitalized adult asthmatics and a second control group of non-hospitalized, adult asthmatics from the same community, mean age of all groups was 33 years. The control groups were matched to cases with respect to age (+-5 years), sex, race, and date of hospitalization or, for community controls, the date of visit to the general practitioner.
Controls and family and friends of cases were interviewed with regard to study variables. Cases had significantly more hospital admissions and more visits to the emergency room, greater frequency of life threatening attacks, poorer compliance, more severe disease, and more psychological problems. Strengths of the Rea study are that it is population based, cases were all the asthmatics who died over a two year period in Auckland, New Zealand and controls were randomly selected from the total population of known asthmatics from the same city during the same time period. Selection bias was reduced and the study has control groups. Weaknesses of this study are that the cases and controls were not matched for severity of disease, and the cases were not available for interview in a manner comparable with controls.

In a study by Strunk et al, 1985, 21 adolescent asthmatics, mean age 13, who died outside the medical center were matched with hospital controls on the basis of age on admission to medical center, sex and severity of disease. Severity of disease was determined by level of corticosteroid used by the patient, or in the extreme case, "any history of respiratory failure requiring ventilation." Fifty-seven physiologic and psychologic variables were analyzed via review of patients' records. Results showed that independently "eight variables could discriminate between the two groups effectively: (1) history of seizures associated with an asthma attack, (2)
conflicts between the patient's parents and the hospital staff regarding medical management of the patient, (3) self-care of asthma while in the hospital was not appropriate for age, (4) prednisone dosage having been decreased by more than 50% during the course of hospitalization, (5) inhaled beclomethasone dipropionate required for treatment, (6) increased asthmatic symptoms during the week preceding discharge, (7) depressive symptoms, and (8) disregard of asthmatic symptoms" (Strunk et al, 1985). Strengths of this study are the case-control method with matching for severity, and considerable efforts to reduce chart rater bias. Weaknesses of this study are the wide range, months to years, between the time of death of the cases and the timing of the analysis of medical center in-patient records. This time gap prevented the researchers from knowledge of events immediately preceding the death. The raters of the patient records were not blinded to the identity of the record as either a case or control. Although the cases and controls were treated equally by not interviewing either group, behavioral data was limited to patient chart review. Many of the behavioral characteristics being taken from the patients' records were not systematically recorded by the hospital staff. This is a problem inherent with retrospective, archival studies.

Risk factors associated with asthma death taken from several studies are condensed into Tables 1 and 2.
<table>
<thead>
<tr>
<th>Table 1. Risk Factors Contributing to Asthma Death</th>
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<td>1) Rea et al, 1986: case-control, n = 44</td>
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<tr>
<td>Recent hospital admission</td>
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<tr>
<td>Recent visit to emergency department</td>
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<tr>
<td>Previous respiratory arrest or near-fatal asthma</td>
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<tr>
<td>Poor medical management</td>
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<tr>
<td>Psychological problems (alcoholism, personality disorder, depression, bereavement, unemployment)</td>
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<tr>
<td>2) Niggeman and Wahn, 1992; case report, n = 3</td>
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<tr>
<td>Poor medication compliance</td>
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<tr>
<td>Psychosocial problems</td>
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<tr>
<td>3) Barriot and Riou, 1987; EMS calls, n = 980</td>
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<tr>
<td>Lack of objective measure of airway obstruction</td>
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<tr>
<td>Medication withdrawal soon after leaving emergency department</td>
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<tr>
<td>4) Strunk, 1989; case-control, n = 21</td>
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<tr>
<td>Inhaled beclomethasone, prednisone decreased by greater than 50% of initial dosage prior to discharge</td>
</tr>
<tr>
<td>History of hypoxic seizure during asthma attacks</td>
</tr>
<tr>
<td>History of respiratory failure requiring intubation and ventilation</td>
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<tr>
<td>Disregard of perceived asthma symptoms</td>
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<tr>
<td>Self care not age appropriate</td>
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<tr>
<td>Manipulative use of asthma</td>
</tr>
<tr>
<td>Parent-child conflict</td>
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<tr>
<td>Family dysfunction or crisis</td>
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<tr>
<td>Psychiatric diagnosis</td>
</tr>
<tr>
<td>Depressive symptoms</td>
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<tr>
<td>Excessive sensitivity to loss or separation</td>
</tr>
<tr>
<td>5) Spitzer et al, 1992; case-control, n = 129</td>
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<tr>
<td>Increased use of beta-agonists albuterol and fenoterol</td>
</tr>
<tr>
<td>6) Fletcher, 1990; case report, n = 35</td>
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<tr>
<td>Long term undertreatment and undersupervision</td>
</tr>
<tr>
<td>Suboptimal management in final illness</td>
</tr>
<tr>
<td>Delay in seeking medical attention</td>
</tr>
<tr>
<td>Inappropriate medical response</td>
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<tr>
<td>Long distance from help</td>
</tr>
<tr>
<td>Precipitous attacks of moderately well controlled asthma</td>
</tr>
</tbody>
</table>
Table 1. (Continued) Risk Factors Contributing to Asthma Death

7) Sears and Rea, 1987; case report, n = 271

- Age: 15-24, >50 y.o.
- Race: Maori, Pacific Islander
- Discontinuity of general practice care
- Delay by patient or relative in seeking help
- Lack of appreciation by patient or family of severity of attack
- Confusion about therapy
- Lack of crises plan
- Use of emergency department rather than regular physician
- Medication non-compliance
- Generally inadequate medical care

8) Benatar, 1986; review article

- Very sudden death
- Outside hospital and at night
- May occur during recovery from acute attack
- Large diurnal variation in airflow obstruction

9) Lenoir, 1987; case report, n = 3

- Severe acute asthma during pre-menstrual or menstrual period
  [n = 3; case report] (Lenoir, 1987)

10) Weiss and Wagener, 1990; USA vital statistics review, n > 50,000 asthma deaths

- Non-white
- Urban
- Poor

11) Rothwell et al, 1987; case report, n = 38

- Maori
- Transport to hospital by car
- Inexperienced emergency department staff
- Delayed transfer to ICU
- Inadequate drug therapy
- Labile peak flows
- Nocturnal deaths

12) Horn et al, 1987; ER complaints, n = 38

- Circadian variation in airflow
<table>
<thead>
<tr>
<th>Table 1. (Continued) Risk Factors Contributing to Asthma Death</th>
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<tr>
<td>13) Williams and Church, 1987; case report, n = 1</td>
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<td>Severe persistent asthma</td>
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<tr>
<td>Misdiagnosis as bronchitis</td>
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<td>Previous acute episode</td>
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<tr>
<td>Patient tolerant of deteriorating symptomology</td>
</tr>
<tr>
<td>Patient failure to use PFR at home</td>
</tr>
<tr>
<td>14) Robin and Lewiston, 1989; case report, n = 4</td>
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<tr>
<td>Idiosyncratic, anaphylactic reaction</td>
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<tr>
<td>Undertreatment of asthma</td>
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<tr>
<td>Aminophylline toxicity</td>
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<tr>
<td>Beta-agonist toxicity</td>
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<tr>
<td>Ventricular arrhythmias</td>
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<tr>
<td>Myocardial contraction band ischemia</td>
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<td>Adrenal insufficiency</td>
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<tr>
<td>Psychological factors</td>
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<tr>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>
Table 2. Risk Factors Not Contributing to Asthma Death

1) Strunk, et al, 1985; case-control, n = 21

- History of respiratory failure requiring ventilation
- Age at onset of wheezing
- Exacerbation/deterioration in disease in year prior to admission
- Pattern of wheezing attacks: sudden deterioration (<8hr) from being well to severe symptoms
- Corticosteroid use in year prior to hospitalization
- History of inhaler abuse
- History of severe exacerbations at night
- Number of hospitalizations in year prior to admission
- Thoracic gas volume
- Forced Expired Volume, 1.0 sec.
- Height, percentile
- Weight, percentile
- Chest findings abnormal other than hyperinflation
- IgE > 95th percentile
- Hemoglobin
- Immediate hypersensitivity skin tests
- Sinusitis on x-ray
- Corticosteroid side effects
- Serum cortisol level
- Wheezing occurring at night or during early morning hours
- Poor perception of wheezing documented in nurses notes
- Admission medications: Prednisone, theophylline, inhaled beclomethasone, inhaled bronchodilator, oral beta-2 agonist
- Discharge medications: same as above + epinephrine
- Psychosocial factors during hospitalization:
  - Emotional exacerbation
  - Poor general assessment (Global Assessment Scale)
  - Panic reactions associated with attacks
  - Exaggeration of illness
  - Denial of seriousness of illness

2) Niggeman, Wahn, 1992; case report, n = 3

- Unrelated to any infectious or allergic process

3) Spitzer, Suissa, et al, 1992; case-control, n = 129

- No risk associated with cromolyn or anti-inflammatory medication

4) Benatar, 1986; review article

- Not necessarily related to prolonged attack
The next case-control study (Crane, et al, 1989) matched 117 cases of asthma death between the ages of 5-45 to four control groups (n = 585) by age, ethnicity, and hospital. The cases comprised all the asthma deaths in New Zealand over a two year period 1981-83. There were four controls for each case. They reported that the relative risk of death in patients taking the drug fenoterol, a beta-agonist, anti-asthma medication, via inhalation to be 1.55 over-all, 2.21 in patients prescribed three or more anti-asthma drugs including fenoterol, 2.16 in patients taking fenoterol with hospital admissions for asthma in the previous 12 months, and 6.45 in patients with prescribed oral corticosteroids and fenoterol. No other asthma drugs were associated with increased relative risk of death from asthma.

This case-control study (Crane, et al, 1989) created such controversy that it directly caused the research published in the following three studies (Grainger, et al, 1990; Pearce, et al, 1989; and Spitzer, et al, 1992) In addition the Crane study stimulated the publication of an article (Horwitz, et al, 1991) discussing the application of case-control methodology to the study of etiologic factors of asthma death. The controversy involved the Crane group implicating the very popular beta-agonist drug, fenoterol, as a risk factor for asthma mortality. Criticism of the Crane study was stimulated by the large drug company that manufactured fenoterol. Asthma
experts around the world were divided over the issue of a potent anti-asthma medication possibly being responsible for increasing asthma mortality. Criticism centered around, "three fundamental flaws - confusion over the underlying clinical question; inadequate classification of and misleading adjustment for asthma severity; and poor standardization of methods for collecting data from cases and controls." (Buist et al, 1989). Apparently, it was thought by the critics that fenoterol may be an insignificant intermediate variable in a larger cause and effect relationship, that asthma severity was an uncontrolled confounding variable, and that using hospital records to gather prescribed drug data for the control group was not consistent with the combination of interviewing general practitioners and archival data collection with respect to the deceased cases. The latter two of these "fundamental flaws" were very weak critical questions because the Crane study group used two techniques to successfully validate their data collection methods, and they went to great length to control for asthma severity. Further criticism (O'Donnell, Rea, Holst, and Sears, 1989) echoed the above and added negative comment regarding the biological plausibility of the Crane study conclusions.
Responding to the criticism the Crane group used the suggestions of the critics and conducted two more case-control studies. The first (Pearce, et al, 1989) improved the study design by obtaining information about prescribed drugs for cases and controls in the same manner. This study reports an over-all odds-ratio of 1.99 for asthma death in patients prescribed inhaled fenoterol. Three other subgroups of patients using fenoterol (fenoterol with two or more other categories of anti-asthma drugs, fenoterol in patients with previous hospital admissions for asthma and fenoterol in patients prescribed corticosteroids) had odds-ratios of asthma death of 2.98, 3.91, and 5.83 respectively. The second study (Grainger, et al, 1990) further refined the case-control study design according to critics suggestions by choosing a control group of patients who had previous hospital admission for asthma in the 12 months preceding the cases death, control group B. An additional four controls, group A, were chosen by the method of their previous studies. Odds-ratio for asthma death of patients using fenoterol was reported to be 2.11 and 2.66 respectively. These findings tend to validate the earlier findings of the Crane group.

"In response to this controversy.....a new study is underway, the Saskatchewan Asthma Epidemiology Project." (Horwitz, et al, 1991) This project was funded by the fenoterol manufacturer. The paper describing the Saskatchewan Asthma
Epidemiology Project outlined an improved methodology for a case-control study and developed the idea that "the difference between death and near-fatal asthma may have little to do with the underlying asthma severity or the pathogenesis of an acute attack. Rather, whether a patient in respiratory failure is resuscitated and the death avoided being related to how rapidly the patients recognized their clinical deterioration and how quickly the patient presented to a center for specialized intensive intervention."

The Saskatchewan project produced a quite different type of case-control study reported by Spitzer et al (1992). These investigators accessed a health insurance database and selected 129 cases of fatal or near-fatal asthma from a cohort of 12,301 asthma patients in Saskatchewan, Canada. Both near-fatal and fatal asthma were recognized as outcome criteria for identification of cases. The cases were matched to controls with respect to place of residence, receipt of social assistance, and previous hospitalization for asthma. All subjects had been prescribed medication for asthma. The results showed that an increased risk of fatal or near-fatal asthma was associated with regular use of beta-adrenergic bronchodilators, especially fenoterol. Odds-ratio for fatal or near-fatal asthma were reported as 5.4 for fenoterol users and 2.4 for albuterol users; thus, confirming the results of the Crane group in New Zealand. Strengths of this study are
the use of the case-control method, the number of subjects, and the unusual circumstance that the project had a peer review committee of eminent international scholars who specialize in the study of asthma. Weaknesses of the study include poor control of confounding variables including medication compliance, and severity of disease. The definition of cases, although concise, seems poorly applied. The investigators did not study any behavioral factors and few social factors. In addition the study did not identify asthma deaths of persons who were not using prescribed medications.

More recently a group from the Netherlands published a study similar to the Saskatchewan Asthma Epidemiology Project using the Dutch community pharmacy database. These results further implicated fenoterol and added use of oral methyl xanthines as a risk factor for acute exacerbations of asthma (Van Ganse, van der Linden, Leufkens, Herings, Vincken and Ernst, 1995).

These excellent studies characterize the few case-control studies that can be found on the epidemiology of asthma fatality and near-fatal asthma.

One case-control study of near-fatal asthmatics with similarly severe controls that examined physiologic, psychologic, and historic variables has been published (Boulet, Deschesnes, Turcotte, and Gignac, 1991). This study of 19 cases and
controls is much like this research. These near-fatal asthmatics were age 20 - 66 years with a mean duration of asthma of 16.3 years. There were eleven men and eight women. Controls were matched for age, sex, atopic status, baseline FEV₁ (forced expired volume during the first one second), and medication use. The authors examined perception of dyspnea (Borg scale), psychological profile (MMPI), an asthma symptom questionnaire, spirometry, diurnal peak expiratory flowrate, and methacholine challenge. They found the near-fatal asthmatics to have increased diurnal variations in peak expiratory flowrate, more poorly controlled asthma with less compliance to treatment, and reduced adaptive personality characteristics. They did not find differences in perception of dyspnea or psychologic profile. This study suffers from a small sample size and potential bias from confounding chronic lung disease often present in the older population. In addition there was no mention of blinding of the investigators or subjects to the identity of cases or controls. The definition of cases in this study was rather broad with one group having endotracheal intubation and mechanical ventilation and another group just having an "acute severe hypercapnia" defined as a $P_aCO_2 > 45$ mm Hg. This definition of hypercapnia, although medically correct, is very liberal. It is difficult to determine how the controls were chosen. This study does not refer to their findings as risk factors as measured "causative" variables occurred after the index event.
PUBLIC HEALTH SIGNIFICANCE

This proposed research is central to the field of public health in that it is an investigation of risk factors of acute, severe exacerbations of a chronic disease stimulated by the presence of an epidemic. It will provide information to aid in the tertiary prevention of disease. It uses the case-control methodology that is a standard tool of public health professionals.

The current asthma epidemic is well documented in medical literature, public health literature and the popular press (Bailey et al, 1992; Consumer Reports on Health, 1992, NHLBI, Executive Summary, 1991). Since it is thought that we have better understanding of the pathophysiology, diagnosis and treatment of asthma (Buist and Vollmer, 1990), expectations are that the morbidity and mortality from asthma should be decreasing or at least remaining constant; however, the converse is true as both are significantly increasing in the U.S.A. (Massachusetts Medical Society, 1995).

Historically public health practitioners have contributed most to the health of the human population by focusing on prevention. Plagues have been quelled and, smallpox has been eradicated through emphasis on prevention. This proposal is focused on the tertiary prevention of fatal asthma. Through better knowledge of etiologic factors of severe asthma
exacerbations the direction for prevention of these severe attacks could be determined. This outcome will contribute to savings in terms of morbidity, mortality and ultimately in human and financial resources.

There could also be major economic and psychological impact related to this type of research in reference to decreasing emergency room and intensive care unit utilization by tens of thousands of asthmatics in acute exacerbations. Clinical experience indicates that there are two to five sudden, near-fatal asthma attacks for every asthma death: therefore, there may be a population numbering between 30 - 120 such cases in Hawaii each year. An emergency room visit will easily cost $1000 for an asthmatic in Hawaii, and intensive care with mechanical ventilation is minimally $5000 per day. The psychological toll is more difficult to assess, but it is a major consideration if one ponders experiencing the loss of physiological homeostasis, lack of physical control, the physically and psychologically invasive high technological environment of emergency and intensive care medicine, the terror of suffocation and the shocking distress of a near-death existence. While the patient, family and health care workers pay most of the psychological cost, much of the
economic cost is passed on to society through increased insurance premiums or through taxes to cover the uninsured.

Since there is increasing asthma mortality in the younger population and increased asthma mortality has been linked to anti-asthma medications. Perhaps it is appropriate to investigate questions about human behavior like, how is the medication compliance, what is the level of social support and what is the psychological status of severe bronchial asthma subjects?
METHODS

Research Question
Are there associations between medication compliance behavior, psychological symptom pattern, social support, and near-fatal exacerbations of asthma in 18 - 46 year old subjects?

Null Hypothesis
Medication compliance behavior will not differ between 18 - 46 year old asthmatics who have near-fatal asthma (cases) and 18 - 46 year old asthmatics who do not have near-fatal asthma (controls).

Psychological symptom pattern will not differ between cases and controls.

Scores on the Provisions of Social Relations Scale (PSR) will not differ between cases and controls.

Study Design
This is a case-control study of asthmatics who have experienced a near-fatal asthma attack. It compares selected historical and behavioral characteristics of the subjects and their respective controls. The study is limited to 19 cases in the State of Hawaii, Island of Oahu during the time period of January 1991 to July 1995. The study is limited to subjects between the ages of 18 and 46 years of age without
regard to gender. This age group is chosen for the relative ease of conducting research with subjects of legal age as well as for the elimination of the developmental variations of younger subjects and the avoidance of most of the chronic cardiopulmonary diseases common among more elderly subjects. The subjects were identified from the hospital records at Kaiser Permanente Health Care System, St. Francis Medical Center, Kuakini Medical Center, St. Francis Medical Center – West, Wahiawa Medical Center, Castle Medical Center, Straub Clinics and Hospital and The Queen's Medical Center. This group of medical centers includes all with active emergency departments and the capacity to perform adult artificial mechanical ventilation on the Island of Oahu with the exception of Tripler Army Medical Center which was not approached because the patient population is often transient and not representative of the population of Hawaii. Kapiolani Medical Center at Pali Momi refused to participate because of a stated perception that research would be an obstacle to United States, Food and Drug Administration approval at that site. Appropriate consent was given by each medical center involved in the study with approval by the hospital research committee or directly from hospital administration. The project was approved by the University of Hawaii, Office of Research Administration, Committee on Human Studies.
The case-control design (Lane-Claypon, 1926) is chosen for this study for a number of reasons. The case-control method is particularly amenable to the study of rare diseases (Doll and Hill, 1952; Gregg, 1945; Lilienfeld, 1956; Sartwell, 1969). While the prevalence of asthma itself is estimated to be 5 - 10% in the U.S.A. (Blanc, 1987; Evans et al, 1987; Rao et al, 1990; Weiss and Wagner, 1990) and 4.03% in Hawaii (Hawaii Health Surveillance Program, 1987), estimated near-fatal asthma attacks are about 1.0 - 1.5 per 10,000 (0.015%) in the State of Hawaii. This estimate is based on chronic lung disease mortality data among 18 - 44 year olds (Department of Health, State of Hawaii, 1988) and clinical experience. Using a cohort study design would require too large a sample to be reasonable for this study. A smaller cohort sample would require follow-up for too long a time period. Case-control studies can test specific hypotheses and demonstrate associations between variables (Cole, 1979; Cornfield, 1952). Although, absolute risk cannot be determined by the case-control method, relative risk can be estimated from odds ratio (Epidemiology Resources, 1984; Ibrahim, 1985; MacMahon and Pugh, 1970; Miettinen, 1976). Case-control studies are often used to search for etiologic factors (Schesselman, 1982).

There are disadvantages to the case-control study. The subjects' memory of exposure or other variables may be inadequate and may introduce recall bias; however, a subject
is rarely likely to report something that did not occur as opposed to fairly easily forgetting what really happened. Thus, the case-control study is limited to some degree because people are basically honest just forgetful. Case-control design cannot be used to measure absolute risk (MacMahon and Pugh, 1970). Attributable risk can be calculated from case-control studies if the incidence of the disease is known in the larger population. The incidence of near-fatal asthma is not known, so this project will not attempt to measure attributable risk. The most serious criticism of case-control studies is the relative comparability of information between cases and controls. In addition, the difficult choice of appropriate cases and controls (Beasley, Pearce, Crane, 1993; Miettinen, 1970) may introduce selection bias. The case-control study design is a good method to study this question if attention is paid to interviewer technique to reduce recall bias and minimize systematic error, use of valid questionnaires and care is taken to reduce selection bias.

The design of this study alters the practice of temporal sequencing using the case-control method where causative factors must precede outcome events. Within the relationships between psychological symptoms, social support, medication compliance and chronic bronchial asthma with its symptom free periods alternating with severe exacerbations there is overlap and feedback loops making temporal sequence difficult to
establish. For example, do psychological symptoms lead to asthma exacerbations or do asthma exacerbations lead to psychological trauma? According to Schlesselman (1982), "this question is difficult to answer because one is dealing with a continuous, evolving process that involves several self-regulating systems with feedback loops." Schlesselman goes on to state, "Occasionally a definite temporal sequence may be difficult to establish, particularly for chronic disease." This unusual use of the case-control method incorporates the following assumption: that near-fatal asthma is a chronic disease state that varies widely in symptomology over time. Observational research cannot claim to prove cause and effect relationships, but it can contribute to better understanding of causality in very complex conditions that do not lend themselves to experimental methods. Therefore, this study does not claim to prove cause and effect relationships. This study is, however, consistent with another case-control study of near-fatal asthma (Boulet et al, 1991) in which cases and controls were given a questionnaire for characteristics of asthma, pulmonary function testing, dyspnea scoring, and psychometric evaluation. These studies compare the cases and controls at the present time, and where differences are found contribute collateral evidence to causality.
Sampling

The population being studied is all the near-fatal asthmatics on the Island of Oahu between the ages of 18 - 46 years during the months between January 1991 and July 1995. It is a sample of the whole as all who met the case definition were included in the study. The sample being studied is that entire population minus military and military dependents and those Oahu residents that utilize Kapiolani Medical Center at Pali Momi. There is no reason to believe that those in the population excluded from the sample create any specific bias. Minimum sample size was not calculated because the values for relative risk of near-fatal asthma and exposure rate among controls (Schlesselman, 1982) is not known.

Cases were chosen using clear, reproducible and strictly applied criteria. Criteria for selection of cases was:

1. Cases had a primary diagnosis of bronchial asthma.
2. Cases experienced respiratory arrest, secondary cardiac arrest, and/or respiratory failure to the point of having endotracheal intubation and placement on continuous mechanical ventilation (CMV).
3. Cases had an onset of the acute asthma attack prior to placement on CMV.
4. Cases will have been successfully removed from CMV within 72 hours from the initiation of CMV.
5. Cases will be of ages 18 - 46 years old.

6. Cases will not have other major confounding diagnosis such as significant cardiac disease or other significant respiratory disease.

Spitzer et al, 1992. defined near-fatal asthma cases as those asthmatics who had "hypercarbia (arterial partial pressure of carbon dioxide above 6.0 kPa [45 mm Hg]), nonelective intubation during an acute asthma attack, or both."

Experience indicates that physicians in Hawaii usually do not place a patient on CMV until the arterial partial pressure of carbon dioxide is considerably above 45 mm Hg. Thus the criteria enumerated above appear more restrictive by comparison.

Cases in this study were identified by searching medical center records for all patients with a primary diagnosis of bronchial asthma who received endotracheal intubation and CMV. The primary or pulmonary physician for each patient was identified so that a control from their medical practice could later be found. All patients identified in this manner were considered potential cases for the study.

Due to variation in medical center record keeping potential cases were identified by different methods at each site, but either method should have captured all the potential cases in
some subjects may not have been identified due to misclassification by medical center personnel responsible for assigning ICD-9 codes in the medical records department or by intensive care unit (ICU) nurses in the ICU. Where possible both methods were used to search for potential cases to cross-check for completeness. Sixty-four (64) cases were identified in this manner, ten (10) of whom had died of asthma prior to contact by the researcher. The origin and disposition of these cases is described in Table 3.

Each case was individually matched with a control. Clear, reproducible, strictly applied criteria for selection of controls was made. Criteria for selection of controls are:

1. Controls will have a primary diagnosis of bronchial asthma.
2. Controls will have been admitted to the hospital with the diagnosis of asthma.
3. Controls will be matched for age within 5 years, gender, hospital discharge asthma medications and pulmonary physician.
4. Controls will not have had an acute near-fatal asthma attack.
5. Controls will not have received CMV for asthma.
6. Controls will not have other significant disease as listed in the criteria for cases above.

Controls were identified by sampling of computer lists of all asthmatic patients of the respective case's primary pulmonary
physician who had been admitted to that medical center during the study time window. The computer searches produced chronological lists of patients' names, medical record numbers, genders, and ages/dates of birth. The index case was found on the list. The next patient down the list chronologically who met the gender/age match became the potential control. If the control chosen did not match the case for medication use or presence of confounding diagnosis, the next appropriate control on the list was chosen. If no control could be found the index case was rejected from the study. Thirteen (13) index cases could not be studied due to failure to identify a matched control. In most circumstances where index cases were rejected in this manner it was the small number of asthmatics treated by that physician limiting the possibility of a matched control.

The medical records of all patients identified as potential cases or controls were thoroughly searched to determine primary diagnosis of bronchial asthma, presence of confounding diagnosis, age, sex, use of endotracheal intubation and CMV, treatment medications, discharge medications, and primary and pulmonary physicians.

After cases and controls were identified each primary or pulmonary physician was contacted and permission was requested
to contact the subjects. Only one physician refused to cooperate with the research project. This resulted in the rejection of two (2) case-control pairs.

Subjects were initially contacted by telephone. The research project was briefly described, and their participation was solicited. Only three cases refused to participate. Reasons for refusal were "not interested" and concern about confidentiality. Seventeen (17) cases could not be reached due to telephone disconnection, telephone change to an unlisted number, moved to the mainland U.S.A., or tourists returning to their home country. One case did not have a telephone and did not respond to contact by mail. If a control could not be contacted, that control was rejected, and another was chosen by the method described above. If no other control was available the corresponding case was rejected.

The subjects who agreed to participate were informed that they would next be contacted by a professional interviewer who would make an appointment.
### TABLE 3. Numbers and Disposition of Cases

<table>
<thead>
<tr>
<th>Medical Center</th>
<th>Cases Identified</th>
<th>Expired</th>
<th>Unable to Contact</th>
<th>Without Control</th>
<th>Refused</th>
<th>Physician Refused</th>
<th>Study Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castle Medical Center</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Kaiser Permanente</td>
<td>11</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Kuakini Medical Center</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>The Queen's Medical Ctr.</td>
<td>17</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>St Francis Medical Ctr.</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>St Francis M.C.- West</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Straub Clinics and Hosp.</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wahiawa General Hospital</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>64</strong></td>
<td><strong>10</strong></td>
<td><strong>17</strong></td>
<td><strong>13</strong></td>
<td><strong>3</strong></td>
<td><strong>2</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>
Instruments

Forms, questionnaires and interview instruments appear in Appendices. These consist of:

ATS-DLD-78 Adult Questionnaire - This standardized questionnaire was developed as part of the Questionnaire Subsection of the Epidemiological Standardization Project of the American Thoracic Society (ATS) and the Department of Lung Disease (DLD) of the National Heart, Lung and Blood Institute, of the National Institutes of Health in 1978 (Ferris, 1978). The ATS-DLD-78 Adult Questionnaire contains queries regarding demographic information, but its focus is lung disease symptoms and history including a brief health history of the subject's parents. This questionnaire has been tested on a sample of 1200 subjects randomly selected from a population of 98,881, estimated to be 87% of the population of Washington County, Maryland (Ferris, 1978).

SCL-90-R - This is a psychological symptom self-report designed to "reflect psychological symptoms patterns of psychiatric and medical patients" (Derogatis, 1977). The results are translated into 9 primary symptom dimensions and 3 global indices of distress. Successful validation of this
instrument developed at The Johns Hopkins School of Medicine has been performed on groups of 1002 psychiatric patients, 974 normal subjects, and 112 adolescent psychiatric outpatients. "The Global Severity Index (GSI) is the best single global score to adopt as an indicator of level of overall distress" (Derogatis, 1977).

The Provisions of Social Relations Scale (PSR) - This instrument for assessing social support was pre-tested on 200 university students (Turner, Frankel and Levin, 1993). It was then validated against 3 other measures of social support in four studies consisting of 312 mothers of newborn infants, 421 persons with acquired hearing loss, 523 discharged psychotic patients, and 989 physically disabled community residents.

Medication compliance - This was comprised of two questions: 1. Do you often medicate yourself in excess of your physician's prescribed anti-asthma regimen? 2. Do you often take less medication than your physician's prescribed anti-asthma regimen?

The results were sorted into four categories, compliant, over medication, under medication, and non-compliant. Over medication and under medication could also be categorized as forms of non-compliance (Klieger, Dirks, 1979).
Data collection
The next contact with the subjects was by a professional interviewer who called by telephone to make an appointment for the interview. The interviewer had a master's degree in social work and specialized in interviewing. The interviewer received training specific to administration of the instruments in this study. Four case/control pairs were interviewed by a Summer research assistant who was trained to administer the instruments in this study.

Interview appointments were made at the subject's convenience to time and place, most often the subject's home or workplace. The interviews took approximately 30 - 40 minutes, and consisted of reading and signing the consent form, and verbally responding to the interviewer's reading of the instruments in Appendix B. Both the interviewer and the subjects were "blinded" to the subjects designation as a case or control. The interviewer was specifically instructed not to discuss the subject's asthma, respiratory condition, or details of the research project not included in the consent form prior to completing the structured questionnaire.
Data analysis

The completed questionnaires were scored, collated and studied using bivariate analysis and chi-squared test for categorical data. ANOVA and t-statistic were used for interval data. In addition to manual calculations a computer program, Epi Info, Version 6 (Dean et al, 1994) was used for data analysis.
RESULTS

Demographic Characteristics

Nineteen cases of near-fatal asthma were comprised of 15 females and 4 males. They were matched for gender, age, asthma severity and primary pulmonary physician with 19 controls. The age of the study group (cases and controls) was fairly evenly distributed between 18 and 46 years with a mean of 32.1 years, standard deviation of 8.75. The level of education was similar between the cases and controls at the same level of education as the of the people of Hawaii, 12.8 years, (University of Hawaii, 1983). Paired analysis of level of education using matched cases and controls showed no statistical differences. At alpha = 0.05 and d.f. = 18 student's two tailed t statistic = -0.519, which was outside the critical region. Household income revealed a wide disparity between a large group at less than $5000/year and a small group at $75,000/year; however, there was no difference between cases, controls (see Table 4). The study group does lag behind the Hawaii's median family income, $42,171 (State of Hawaii, Department of Business, Economic Development and Tourism, 1993).
TABLE 4. Demographic Characteristics

<table>
<thead>
<tr>
<th>Education (Years)</th>
<th>Cases</th>
<th>MEAN</th>
<th>SD</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.6</td>
<td>1.8</td>
<td>10 - 17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>13.0</td>
<td>1.8</td>
<td>12 - 18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Income (Household dollars/year)</th>
<th>Cases</th>
<th>MEAN</th>
<th>SD</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12,500</td>
<td>7,500</td>
<td>&lt;5,000-75,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>10,000</td>
<td>7,500</td>
<td>&lt;5,000-75,000</td>
</tr>
</tbody>
</table>

*no difference at 5% level of significance

Forty-seven percent of cases and thirty-two percent of controls are married. Difference in marital status is not statistically significant (see Table 5). There are no differences in ethnicity between cases and controls at the 5% level of significance, but the percentage of Hawaiians in this study is approximately triple the 11% seen in the general population of Oahu (University of Hawaii, 1983). These unusual ethnicity numbers for severe asthmatics are similar to population statistics for asthma in the State of Hawaii (American Lung Association of Hawaii, 1993), (see Table 6).

Table 5. Marital Status, Matched Analysis

<table>
<thead>
<tr>
<th>Number of Married Controls</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA Married</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>NFA Single</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Chi-square = 0.57, p = 0.45
Table 6. Ethnicity and Asthma

(percentage population or sample)

<table>
<thead>
<tr>
<th></th>
<th>Hawa</th>
<th>Cauc</th>
<th>Japn</th>
<th>Chin</th>
<th>Fili</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects in this study</td>
<td>34.8</td>
<td>26.3</td>
<td>15.8</td>
<td>7.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Asthmatics in Hawaii*</td>
<td>35.0</td>
<td>17.6</td>
<td>11.1</td>
<td>3.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Population, Island of Oahu+</td>
<td>11</td>
<td>33</td>
<td>25</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Population, State of Hawaii+</td>
<td>12</td>
<td>33</td>
<td>25</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>

*(American Lung Association of Hawaii, 1993)
+*(University of Hawaii, 1983)

Risk Factors of Primary Focus

Medication compliance questions produced two levels of response. One level is simply two categories, compliant or non-compliant, with bivariate analysis of a 2 X 2 contingency table. This bivariate analysis produced a statistically significant odds ratio of 5.93 (see Table 7).

Table 7. Medication Compliance, Matched Analysis

<table>
<thead>
<tr>
<th>Number of Controls</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA Non-Compliant</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>NFA Compliant</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Odds ratio = 8.00, Chi-square = 5.44
CI = 1.28 - 178.95 with p = 0.019

NFA = near-fatal asthma
This result requires rejection of the null hypothesis with the outcome being the reverse of conventional thought, i.e., near-fatal asthmatics having poorer medication compliance. The second level uses four categories of response including compliant, under medication, over medication or both. Here each category may be looked at separately in a 4 X 2 table. The 4 X 2 table interestingly shows a disproportionate number of compliant cases and under medicating controls; although, the results are not statistically significant at 5% level of significance; they are at 10% level of significance (see Table 8). This may provide explanation for the 2 X 2 table, Table 7, results. The explanation may be that nearly all the near-fatal asthmatics, 84%, took their asthma medications as often as prescribed or in excess of their prescription. Most of the controls, 68%, took their medications less often than prescribed by their physician.

Table 8. Medication Compliance, 4 X 2 Table Analysis

<table>
<thead>
<tr>
<th>Near-fatal Asthma</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Under medication</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Over medication</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Both over and under medication</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Chi-square = 6.54, p = 0.088 with df = 3.
Psychological symptoms expressed by the SCL-90-R, Global Severity Index (GSI) score did not vary significantly between cases and controls; thereby, requiring failing to reject the null hypothesis (see Table 8). When the GSI was converted to a categorical variable by designating each subject as "normal" or "distressed" there was no significant variation between cases and controls (see Table 9). The study group, cases and controls, did vary significantly from the normal. The upper limit normal T score = 55; mean T score = 31 (Derogatis. 1977). This study group, cases and controls had a mean T score = 65.5 with 87% of the subjects being distressed.

The data from the Provisions of Social Relations scale showed no significance at the 5% level of significance, Table 8, requiring failure to reject the null hypothesis. Dr. B. Gail Frankel, one of the authors of this scale, stated that there is no clear dividing point to determine adequate social support (Frankel 1995); therefore, conversion to a categorical variable was not well advised.

Further analysis of SCL-90 and PSR results using paired data of matched cases and controls provides a better perspective of this relationship. Using the student's two-tailed t test alpha = 0.05 and d.f. = 18 both comparisons fall outside the critical region and fail to reject the null hypothesis (SCL-90, t = -1.19 and PSR, t = -0.89).
Table 9. Results of SCL-90-R and PSR Scale

<table>
<thead>
<tr>
<th></th>
<th>MEAN</th>
<th>SD</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychologic Symptom Pattern</strong> (GSI T-score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>63</td>
<td>9.8</td>
<td>44 - 81</td>
</tr>
<tr>
<td>Controls</td>
<td>68</td>
<td>8.3</td>
<td>45 - 81</td>
</tr>
<tr>
<td><strong>Provision of Social Relations</strong> (Total score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>26.3</td>
<td>8.9</td>
<td>15 - 44</td>
</tr>
<tr>
<td>Controls</td>
<td>29.2</td>
<td>8.8</td>
<td>16 - 45</td>
</tr>
</tbody>
</table>

No difference at 5% level of significance
p value = 0.21, +p value = 0.32

Table 10. SCL-90-R Results as a Dichotomous Variable

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Distressed</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

Odds ratio = 0.26, Chi-square = 2.05
CI = 0.04 - 1.47 with p = 0.15

Respiratory Symptom Data

Differences between cases and controls were insignificant at the 5% level of significance for the following chronic conditions: wheeze, breathlessness, cough, and phlegm production (see Tables 11 - 14).
Table 11. Wheezing, Most Days and Nights, Matched Analysis

<table>
<thead>
<tr>
<th>Number of Wheezing Controls</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA Wheezing</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>NFA Negative</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Chi-square = 2.00, p = 0.16

Table 12. Breathlessness, Matched Analysis

<table>
<thead>
<tr>
<th>Number of Controls Breathless</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA with Breathlessness</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>NFA Negative</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Chi-square = 0.67, p = 0.41

Table 13. Chronic Cough, Matched Analysis

<table>
<thead>
<tr>
<th>Number of Controls with Chronic Cough</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA with chronic cough</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>NFA Negative</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Chi-square = 1.67, p = 0.20

Table 14. Phlegm Production, Matched Analysis

<table>
<thead>
<tr>
<th>Number of + controls</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA Phlegm, most days</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

Chi-square = 0.07, p = 0.79
**Historical Data**

Differences between cases and controls were insignificant or irrelevant at the 5% level of confidence for the following historical variables: age of asthma onset, Father's asthma, Mother's asthma, dusty occupation, cigarette smoking, hayfever and pneumonia (see Tables 15 - 20). Sixty percent (60.5%) of the subjects had at least one parent with asthma. This is much higher than the 20% expected. The expected value is estimated from the approximate prevalence of asthma, which is about 10%, on the Island of Oahu. The mean duration of asthma (age minus age at asthma onset) among the cases is 22.5 years and among the controls is 20.6 years.
Table 15. Age of Asthma Onset, Matched Pairs

Age at Asthma Onset

<table>
<thead>
<tr>
<th>CC#</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>16</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>17</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean difference = -0.684 years
Student's two-tailed t = -0.17
with alpha = 0.05 and d.f. = 18

Table 16. Dusty Occupation, Matched Analysis

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA Dusty, occupation</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>NFA Negative</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Chi-square = 0.44, p = 0.50
### Table 17. Cigarette Smoking Now, Matched Analysis

<table>
<thead>
<tr>
<th>Number of Smoking Controls</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA now smoking</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>NFA not smoking</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

Chi-square = 0.14, p = 0.71

### Table 18. History of Cigarette Smoking, Matched Analysis

<table>
<thead>
<tr>
<th>Number of Controls Who Smoked</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFA, Hx of smoking</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>NFA never smoked</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Chi-square = 0.08, p = 0.77
Table 19. Hayfever, Matched Analysis

<table>
<thead>
<tr>
<th></th>
<th>Number of Controls with Hayfever</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>NFA with hayfever</td>
<td>4</td>
</tr>
<tr>
<td>NFA Negative</td>
<td>3</td>
</tr>
</tbody>
</table>

Chi-square = 0.17, p = 0.68

Table 20. Pneumonia, Matched Analysis

<table>
<thead>
<tr>
<th></th>
<th>Number of Controls with Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>NFA with pneumonia</td>
<td>9</td>
</tr>
<tr>
<td>NFA Negative</td>
<td>2</td>
</tr>
</tbody>
</table>

Chi-square = 0.57, p = 0.44
Qualitative Results

There are several areas of qualitative observations.

1. The subjects of this study were with few exceptions on appropriate anti-asthma medications (see Tables 21 and 22).

Table 21. Current Asthma Medications

<table>
<thead>
<tr>
<th></th>
<th>n = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-agonist</td>
<td>35</td>
</tr>
<tr>
<td>Steroid</td>
<td>29</td>
</tr>
<tr>
<td>Theophylline</td>
<td>26</td>
</tr>
<tr>
<td>Cromolyn</td>
<td>8</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>2</td>
</tr>
</tbody>
</table>

*Subjects were matched for anti-asthma medications at hospital discharge

Table 22. Generic Names of Medications in Each Class

<table>
<thead>
<tr>
<th>Beta-agonists:</th>
<th>Theophylline:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>Slo-BID'</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Theodur'</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>Uniphyl'</td>
</tr>
<tr>
<td>Salmeterol</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Steroids:</th>
<th>Cromolyn:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>Cromolyn Na</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Nedocromil Na</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
</tr>
<tr>
<td>Trimicinolone</td>
<td>Anticholinergic:</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Ipratropium Br</td>
</tr>
</tbody>
</table>

*Brand name
2. Seventeen of nineteen cases were seeing a physician specialist for pulmonary medicine.

3. A large number of cases identified for study died between the time of the index event and contact by the researcher. This study underestimates the actual number of these deaths which exceeds 16% of those identified (see Table 3). Underestimation occurred because some medical centers did not list patients who expired on the computer search reports; therefore, the index near-fatal event was not found because of their subsequent asthma mortality.

4. Pulmonary medical care of many of the cases and controls is fragmented. The physicians frequently complained that these patients did not follow-up hospital admissions with office visits. The same subjects often appeared in the database of more than one medical center or under the care of more than one physician.

5. There is disparity of numbers of near-fatal asthmatics in the caseloads of pulmonary physicians on the Island of Oahu.

6. Oahu physicians are very cooperative with basic research.

7. There is a lack of good record keeping and record retrieval by most care medical centers on the Island of Oahu. Data collection during this project was hampered by missing data from medical center records, and numerous problems retrieving existing records due unavailable medical records personnel, medical records personnel unable to operate retrieval system and/or the "computer" not working for various reasons.
DISCUSSION

Briefly, this study generates new knowledge to aid understanding risk factors of near-fatal asthma both by comparison of the near-fatal asthmatics to the controls and by revealing characteristics of a group of severe asthmatics, both the cases and controls. Major findings by comparing cases and controls are differences in medication compliance patterns between near-fatal asthmatics and their controls. There are few other differences between near-fatal asthmatics and similarly severe asthmatics who have had hospital admission for asthma. As a group, cases and controls, these subjects are more often low income, psychologically distressed, female, and of Hawaiian ethnicity who are seeing a pulmonary medicine physician and being prescribed appropriate medications. Subjects frequently have at least one parent with asthma. Mean duration of asthma is 21.5 years. While being on appropriate medications (steroid, beta-agonist and theophylline compound) and seeing a pulmonary specialist near-fatal asthmatics have an excessive mortality rate at this relatively young age. A more detailed discussion of each of these results follows.

Poor medication compliance of cases and controls shown here is similar to other asthma studies (Kinsman, Dirks, Dahlem, 1980; Klieger, Dirks, 1979; Patterson, Greenberger, Patterson, 1991; Voyles, Menendez, 1983). There is clear evidence in other
studies that medicating with beta-agonists is linked to increased asthma mortality (Beaglehole et al, 1987; Beasley et al, 1994; Burgess et al, 1994; Crane et al, 1992; Crane et al, 1989; Grainger et al, 1991; Pearce et al, 1990; Rea et al, 1986; Spitzer et al, 1992; Suissa et al, 1994). That these controls have significantly poorer compliance than near-fatal asthmatics, particularly under medicating themselves, may help explain the controversy surrounding the use of beta-agonists and asthma mortality. It is plausible that restraint in using anti-asthma medications by these severe, under medicating asthmatics (controls) somehow protects them from near-fatal episodes or asthma death. Numerous studies have found beta-agonist use linked to asthma death; although, no mechanism has been specifically described. Therefore, finding under medication associated with a lack of near-fatal attacks is not surprising. One difficulty in acceptance of this idea is that not following the physician's prescription may be advantageous.

This may be the first study directly pointing to restraint in anti-asthma medication use as being beneficial; however, other excellent studies approach this concept. Sears, Taylor and Print (1990) associate negative health outcomes to regular use of beta-agonists in bronchial asthma patients. Suissa et al,
(1994) conclude that "increasing use of beta-agonist inhalers.....is a major predictive factor of unfavourable outcomes in asthma."

There remains a question about these results regarding whether the respondents are reporting beta-agonist under medication or another anti-asthma drug. This is an important question for two reasons. First, the medication compliance questions in these interviews ask about anti-asthma medications generally, not beta-agonists specifically. In my professional experience patients refer to their beta-agonist medication in response to this type of question; because, the beta-agonists provide easily recognized relief from shortness of breath in a matter of a few minutes. Second, it is true that bronchial asthma patients often under medicate with their corticosteroid and cromolyn compound medications; because, these medications only offer relief from shortness of breath over a period of days or at best several hours. Because the positive effects of corticosteroids and cromolyn compounds cannot be easily recognized, the asthmatic may not see immediate value in taking their prescription.

Another aspect of the medication compliance results of this study is that the physician's of these subjects sometimes prescribed the beta-agonist "as needed" with an upper limit on the number of "puffs" and frequency of administration. In this
situation the asthmatic may not take their beta-agonist for weeks, but would still, reasonably report themselves as compliant. This type of prescription reduces the number of subjects that might report under medication or under medication-like behavior in this study. Thus, the effect of under medication with anti-asthma medications may be more significant than shown here.

The lack of any other differing characteristics between the cases and controls in this study may point to better case/control definition in future studies of risk factors of near-fatal asthma. Perhaps near-fatal asthmatics and similarly severe asthmatics as defined in this study could be used as a single group of cases. Results from literature reviewed (Campbell et al, 1994; Richards et al, 1993) suggest that choosing, as controls, asthmatics who have not been admitted to the hospital may provide greater variation with regard to potential risk factors. If this is done, care will need to be taken by researchers because of confounding by disease severity.

In concurrence with other reports (Boulet et al, 1991; Campbell et al, 1994; Dirks, Jones, Fross, 1979; Fritz, Rubenstein, Lewiston, 1987; Miller, 1987) 87% of the subjects in this study demonstrate significant psychological symptoms; although, there is little difference between cases and
controls. It is very difficult to determine the temporal sequence of this relationship; because, a life threatening or suffocating disease can cause psychological distress. Concomitantly psychological distress triggers asthma exacerbations. The level of psychological distress may also be related to low income in many of the subjects.

Like other studies (Mitchell, 1991; Weiss and Wagener, 1990; Wissow, Warshow, Box, Baker, 1988) low income groups and certain disadvantaged minorities seem to be disproportionately afflicted. This study does not reveal any clear explanation for these observations. The interviewer stated a subjective observation that the household and lifestyle of the subjects seems normal. It is difficult to imagine maintenance of "normality" at this income level; however, it is easy to imagine that regular employment and job promotion might be difficult for a person with severe asthma. Many of these subjects were unemployed. The disproportionate number of Hawaiians with severe asthma is consistent with asthma prevalence in Hawaii. Complex socioeconomic relationships involving culture and history with regard to ethnicity and asthma have not been resolved in the U.S.A. or other developed countries, (Rothwell et al, 1987; Sears and Rea, 1987; Targonski, Persky, Orris and Addington, 1994; Weiss and
Wagener, 1990). Ethnicity was determined by taking the first response to the question, "What is your ethnicity?" Part-Hawaiian was combined with Hawaiian.

The large number of females (79%) among the near-fatal asthmatics is remarkable as the American Lung Association of Hawaii (1993) reports an age group, 17 - 44 years, male/female asthma prevalence ratio in Hawaii of 1/1.22. This result is opposite the findings of Boulet et al (1991) whose 19 subjects were 58% males. This result cannot be attributed to selection bias as 75% (48/64) of the cases identified initially were female. The male/female ratio changed little through attrition in the selection process.

The age of asthma onset was determined by asking the subject, "At what age did it (asthma) start?" Many replied, since "birth." It is doubtful that infants had a diagnosis of asthma (Gergen, Mulally and Evans, 1988), but it is likely that these subjects had asthma attacks among their earliest memories. Regardless whether the asthma began at birth or 3 - 5 years of age, duration of asthma of 21.5 years for asthmatics between the ages of 18 - 46 years means most subjects had asthma most of their lives.
It is encouraging that the subjects of this research seem to be accessing appropriate health care. The index cases in this study were identified in medical center records which may seem to imply this observation; however, that is not necessarily the case as anyone, regardless of appropriateness of medical care, who is dying of an acute exacerbation of asthma will be ultimately taken to a medical center intensive care unit and be appropriate for inclusion in this study. It may be argued that those who died of asthma during an acute exacerbation and did not become eligible to be in this study may have had less appropriate medical care. Appropriateness of medical care of the controls in this study is obvious as they were matched to the cases for physician practice and medical center. In at least some cases the pulmonary specialist was consulted only during the acute exacerbation and was not seen for out-patient follow-up. With others there was a very close, professional relationship. This study did not address the quality of the relationship of the asthmatic and the pulmonary specialist.

The unequal distribution of near-fatal asthmatics among the caseload of active pulmonary physicians on the Island of Oahu has many possible explanations including the size of the individual physician's practice, geographic location, quality of patient care, and the style of patient care. The style of patient care could include factors like exclusion criteria, such as refusal to accept cigarette smokers, inclusion
criteria, such as encouragement of certain ethnic, age or income groups, focus on patient behavior changes, patient follow-up and many other factors not addressed in this project.

Medical record keeping and retrieval is less than optimal at most of the acute care medical centers on the Island of Oahu. For example, a large medical center with an active emergency room failed to produce any record of near-fatal asthma admissions on three successive computer searches; at the same time the intensive care unit logbook had been lost. Basically the acute care medical centers, with one exception, did not know the identity of, or current address or medication use of the bronchial asthma patients visiting the institution. This observation may become of more interest if national trends toward managed care continue. To emphasize this point the patient data was much more up-to-date and accessible at the one H.M.O. involved in this research in spite of the institutional review board at the H.M.O. being one of the most stringent.

It is shocking, though not surprising, to observe the frequent mortality of the potential cases for this study. It was not within the scope of this research to investigate the untimely deaths of potential subjects.
The results of this study were limited by the small sample size. The small sample was due largely to difficulty
gleaning all potential cases from the hospital records, inability to contact potential cases and controls, mortality
of the cases, and rejection of cases due to lack of a matching control. In addition, the age limitation of this study
immediately disqualified the majority of near-fatal asthmatics from entering the study as most near-fatal asthmatics were
older. A larger sample size would increase the probability of significant variance while providing the opportunity to
statistically partition the variance (Mantel and Haenszel, 1959) perhaps, revealing the nature of the interdependent
relationships between causation variables.

Medication compliance is an intricate question that could be further investigated by inquiring into the reasons for over or
under medication, by asking which medications are more often involved in non-compliant behavior, and what criteria do
asthmatics consider to be more important than following their physician's advice?

Questions more closely relating near-fatal asthma attacks and social support could be asked specific to perceptions of life
threatening illness, existence of plans to seek medical
attention in the event of severe respiratory distress, and appropriateness of peak expiratory flowmeter usage. This type of inquiry might include factors related to income like ownership of a prescription drug plan, medical insurance, or even a functional automobile.

The observations regarding gender and parental asthma deserve further research.

This research supports the hypothesis that there is little difference between severe asthmatics, near-fatal asthmatics and those who die of asthma (Beasley, Pierce, Crane, 1993; Campbell et al 1993; Richards, Kolbe, Fenwick, Rea, 1993; Ruffin, Latimer and Schembri, 1991). It may be time to follow cohorts of severe and near-fatal asthmatics in prospective studies (Ruffin et al, 1991). The number of relatively young people observed to be dying of asthma is a mandate to pursue more knowledge of fatal and near-fatal asthma risk factors.
APPENDIX A

EPIDEMIOLOGY STANDARDIZATION PROJECT

ATS-DLD-78-A

1. Date of Birth: ___ ___ ___
   Month Day Year

2. Place of Birth: ___________________________________

3. Sex:
   1. Male____
   2. Female____

4. What is your marital status?
   1. Single____
   2. Married____
   3. Widowed____
   4. Separated/Divorced____

5. What is your ethnicity?
   ___________________________________

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

6B. Estimate your income:
   1. Less than $5,000____
   2. $5,000 - $9,999____
   3. $10,000 - $14,999____
   4. $15,000 - $24,999____
   5. $25,000 - $34,999____
   6. $35,000 - $49,999____
   7. $50,000 - $74,999____
   8. $75,000 - $99,999____
   9. $100,000 - $149,999____
   10. $150,000 or more____
These questions pertain mainly to your chest. Please answer yes or no if possible. If a question does not appear to be applicable to you, check the does not apply space. If you are in doubt about whether your answer is yes or no, record no.

Card Number

Cough

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

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

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

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

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

E. Do you usually cough like this on most days for 3 consecutive months or more during the year?
   1. Yes 2. 
   8. Does not apply

F. For how many years have you had this cough?

   Number of years
   88. Does not apply
PHLEGM

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

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

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

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

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

E. Do you bring up phlegm like this on most days for 3 consecutive months or more during the year?
1. Yes____ 2.____
  8. Does not apply____

F. For how many years have you had trouble with phlegm?
Number of years
  88. Does not apply____
**EPISODES OF COUGH AND PHLEGM**

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

1. Yes__ 2. No__

IF YES TO 9A:

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

____________________________

Number of years

88. Does not apply__

**WHEEZING**

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

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

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

B. For how many years has this been present?

____________________________

Number of years

88. Does not apply__

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

1. Yes__ 2. __

IF YES TO 11A:

B. How old were you when you had your first such attack? __________ Age in years

88. Does not apply__

C. Have you had 2 or more such episodes? 1. Yes__ 2. No__

8. Does not apply__

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

1. Yes__ 2. No__

8. Does not apply__
BREATHLESSNESS

12. If disabled from walking by any condition other than heart or lung disease, please describe and proceed to Question 14A. Nature of condition(s):______________________________

13A. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?
   1. Yes____ 2. No____

IF YES TO 13A:

B. Do you have to walk slower than people of your age on the level because of breathlessness?
   1. Yes____ 2. No____
     8. Does not apply____

C. Do you ever have to stop for breath when walking at your own pace on the level?
   1. Yes____ 2. No____
     8. Does not apply____

D. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level?
   1. Yes____ 2. No____
     8. Does not apply____

E. Are you too breathless to leave the house or breathless on dressing or undressing?
   1. Yes____ 2. No____
     8. Does not apply____
CHEST Colds and Chest Illness

14A. If you get a cold, does it usually go to your chest? (Usually means more than \( \frac{1}{2} \) the time.)
   1. Yes____ 2. No____
   3. Don't get colds____

15A. During the past 3 years, have you had any chest illness that have kept you off work, indoors at home, or in bed?
   1. Yes____ 2. No____

IF YES TO 15A:

B. Did you produce phlem with any of these chest illness?
   1. Yes____ 2. No____
   8. Does not apply____

C. In the last 3 years, how many such illnesses, with (increased) phlem, did you have which lasted a week or more?
   Number of illness
   ____ No such illness
   8. Does not apply____

Past Illness

16. Did you have any lung trouble before the age of 16?
   1. Yes____ 2. No____

17. Have you ever had any of the following?
   1A. Attacks of bronchitis?
      1. Yes____ 2. No____

   IF YES TO 1A:
   B. Was it confirmed by a doctor? 1. Yes____ 2. No____
      8. Does not apply____
   C. At what age was your first attack? ____ Age in years
      88. Does not apply____
2A. Pneumonia (include bronchopneumonia)?
   1. Yes  
   2. No

IF YES TO 2A:
B. Was it confirmed by a doctor? 
   1. Yes  
   2. No

C. At what age did you first have it? 
   ____ Age in years

3A. Hay fever?
   1. Yes  
   2. No

IF YES TO 3A:
B. Was it confirmed by a doctor? 
   1. Yes  
   2. No

C. At what age did it start? 
   ____ Age in years

18A. Have you ever had chronic bronchitis?
   1. Yes  
   2. No

IF YES TO 18A:
B. Do you still have it? 
   1. Yes  
   2. No

C. Was it confirmed by a doctor? 
   1. Yes  
   2. No

D. At what age did it start? 
   ____ Age in years

19A. Have you ever had emphysema?
   1. Yes  
   2. No

IF YES TO 19A:
B. Do you still have it? 
   1. Yes  
   2. No

C. Was it confirmed by a doctor? 
   1. Yes  
   2. No

D. At what age did it start? 
   ____ Age in years
20A. Have you ever had asthma? 1.Yes____ 2.No____

IF YES TO 20A:

B. Do you still have it? 1.Yes____ 2.No____
8. Does not apply____

C. Was it confirmed by a doctor? 1.Yes____ 2.No____
8. Does not apply____

D. At what age did it start? ____ Age in years
88. Does not apply____

E. If you no longer have it, at what age did it stop? ____ Age stopped
88. Does not apply____

F. What anti-asthma medications are you currently taking?

G. Do you often medicate yourself in excess of your physician's prescribed anti-asthma regimen? 1.Yes____ 2.No____

H. Do you often take less medication than your physician's prescribed anti-asthma regimen? 1.Yes____ 2.No____

21. Have you ever had:

A. Any other chest illness? 1.Yes____ 2.No____
If yes, please specify______________________________

B. Any chest operations? 1.Yes____ 2.No____
If yes, please specify______________________________
C. Any chest injuries?  
1. Yes___  2. No___  
If yes, please specify__________________________________________

22A. Has a doctor ever told you that you had heart trouble?  
1. Yes___  2. No___  
IF YES TO 22A:  
B. Have you ever had treatment for heart trouble in the past 10 years?  
1. Yes___  2. No___  
8. Does not apply___

23A. Has a doctor ever told you that you had high blood pressure?  
1. Yes___  2. No___  
IF YES TO 23A:  
B. Have you ever had treatment for high blood pressure (hypertension) in the past 10 years?  
1. Yes___  2. No___  
8. Does not apply___
OCCUPATIONAL HISTORY

24A. Have you ever worked full time (30 hours per week or more) for 6 months or more?
   1. Yes___ 2. No___

IF YES TO 23A:

B. Have you ever worked for a year or more in any dusty job?
   1. Yes___ 2. No___ 8. Does not apply___
   Specify job/industry__________________________
   Total years worked__________________________

C. Have you ever been exposed to gas or chemical fumes in your work?
   1. Yes___ 2. No___
   Specify job/industry__________________________
   Total years worked__________________________

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

25A. Have you ever smoked cigarettes? (No means less than 20 packs of cigarettes or 12 oz of tobacco in a lifetime or less than 1 cigarette a day for 1 year.)
1. Yes____ 2. No____

IF YES TO 25A:

B. Do you smoke cigarettes (as of 1 month ago)?
1. Yes____ 2. No____
8. Does not apply____

C. How old were you when you first started regular cigarette smoking?
_______ Age in years
88. Does not apply____

D. If you have stopped smoking cigarettes completely, how old were you when stopped?
____ Check if still smoking
88. Does not apply____

E. How many cigarettes do you smoke per day now?
____ Cigarettes per day
88. Does not apply____

F. On the average of the entire time you smoked, how many cigarettes did you smoke per day?
____ Cigarettes per day
88. Does not apply____

G. Do or did you inhale the cigarette smoke?
1. Does not apply____
2. Not at all____
3. Slightly____
4. Moderately____
5. Deeply____
26A. Have you ever smoked a pipe regularly?  
1. Yes  
2. No  
**IF YES TO 26A: FOR PERSONS WHO HAVE EVER SMOKED A PIPE**

B. 1. How old were you when you started to smoke a pipe regularly?  
____  
Age

2. If you have stopped smoking a pipe completely, how old were you when you stopped?  ____  
Age stopped
Check if still smoking pipe ____  
88. Does not apply ____

C. On the average over the entire time you smoked a pipe, how much pipe tobacco did you smoke per week?  
____oz per week  
(A standard pouch of tobacco contains 1.5 oz)  
88. Does not apply ____

D. How much pipe tobacco are you smoking now?  
____oz per week  
88. Not currently smoking a pipe____

E. Do or did you inhale the pipe smoke?  
1. Never smoked____  
2. Not at all____  
3. Slightly____  
4. Moderately____  
5. Deeply____
27A. Have you ever smoked cigars regularly?  
1. Yes_  
(Yes means more than 1 cigar a week for a
year.)  
2. No___  

IF YES TO 27A: FOR PERSONS WHO HAVE EVER SMOKED CIGARS

B. 1. How old were you when you started smoking cigars regularly?  
____ Age

2. If you have stopped smoking cigars completely, how old were you when you stopped? ____ Age stopped  
Check if still smoking cigars ____  
88. Does not apply ____

C. On the average over the entire time you smoked cigars, how many cigars did you smoke per week?  
____ Cigars per week  
88. Does not apply ____

D. How many cigars are you smoking per week now?  
____ Cigars per week  
88. Check if not smoking cigars currently____

E. Do or did you inhale the cigar smoke?  
1. Never smoked___  
2. Not at all___  
3. Slightly___  
4. Moderately___  
5. Deeply___
FAMILY HISTORY

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

<table>
<thead>
<tr>
<th></th>
<th>FATHER</th>
<th>MOTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Chronic Bronchitis?</td>
<td>1. YES 2. NO 3. DON'T</td>
<td>1. YES 2. NO 3. DON'T</td>
</tr>
<tr>
<td>B. Emphysema?</td>
<td>1. YES 2. NO 3. DON'T</td>
<td>1. YES 2. NO 3. DON'T</td>
</tr>
<tr>
<td>C. Asthma?</td>
<td>1. YES 2. NO 3. DON'T</td>
<td>1. YES 2. NO 3. DON'T</td>
</tr>
<tr>
<td>D. Lung cancer?</td>
<td>1. YES 2. NO 3. DON'T</td>
<td>1. YES 2. NO 3. DON'T</td>
</tr>
<tr>
<td>E. Other chest conditions?</td>
<td>1. YES 2. NO 3. DON'T</td>
<td>1. YES 2. NO 3. DON'T</td>
</tr>
</tbody>
</table>

28A. Is parent currently alive?

<table>
<thead>
<tr>
<th></th>
<th>FATHER</th>
<th>MOTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Please specify</td>
<td>8. Don't know</td>
<td>8. Don't know</td>
</tr>
</tbody>
</table>

C. Please specify cause of death.

_____________________________
APPENDIX B, SCL-90-R

INSTRUCTIONS
Below is a list of problems and complaints that people sometimes have. Read each one carefully, and select one of the numbered descriptors that best describes HOW MUCH DISCOMFORT THAT PROBLEM CAUSED YOU DURING THE PAST MONTH INCLUDING TODAY. Place that number in the open space to the right of the problem. Do not skip any items, and print your number clearly. If you change your mind, erase your first number completely. Read the example below before beginning, and if you have any questions please ask the technician.

<table>
<thead>
<tr>
<th>HOW MUCH WERE YOU DISTRESSED BY:</th>
<th>Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Not at all</td>
</tr>
<tr>
<td>Ex. Body Aches...................</td>
<td>1 A little bit</td>
</tr>
<tr>
<td></td>
<td>2 Moderately</td>
</tr>
<tr>
<td></td>
<td>3 Quite a bit</td>
</tr>
<tr>
<td></td>
<td>4 Extremely</td>
</tr>
</tbody>
</table>

1. Headaches...........................
2. Nervousness or shakiness inside...................................
3. Repeated unpleasant thoughts that won't leave your mind...................................
4. Faintness or dizziness..................................
5. Loss of sexual interest or pleasure..................................
6. Feeling critical of others..................................
7. The idea that someone else can control your thoughts..
8. Feeling others are to blame for most of your troubles.
9. Trouble remembering things..................................
10. Worried about sloppiness or carelessness..........................
11. Feeling easily annoyed or irritated..........................
12. Pains in heart or chest..................................
13. Feeling afraid in open spaces or on the streets............
14. Feeling low in energy or slowed down..........................
15. Thoughts of ending your life..........................
16. Hearing voices that other people do not hear............
17. Trembling..................................
18. Feeling that most people cannot be trusted..................
19. Poor appetite..................................
20. Crying easily..................................
21. Feeling shy or uneasy with the opposite sex..................
22. Feelings of being trapped or caught..........................
23. Suddenly scared for no reason..................................
24. Temper outbursts that you could not control..............
25. Feeling afraid to go out of your house alone..................
26. Blaming yourself for things..................................
27. Pains in lower back..................................
28. Feeling blocked in getting things done.....................
29. Feeling lonely
30. Feeling blue
31. Worrying too much about things
32. Feeling no interest in things
33. Feeling fearful
34. Your feelings being easily hurt
35. Other people being aware of your private thoughts
36. Feeling others do not understand you or are unsympathetic
37. Feeling that people are unfriendly or dislike you
38. Having to do things very slowly to insure correctness
39. Heart pounding or racing
40. Nausea or upset stomach
41. Feeling inferior to others
42. Soreness of your muscles
43. Feeling that you are watched or talked about by others
44. Trouble falling asleep
45. Having to check and double check what you do
46. Difficulty making decisions
47. Feeling afraid to travel on buses, subways, or trains
48. Trouble getting your breath
49. Hot or cold spells
50. Having to avoid certain things, places or activities because they frighten you
51. Your mind going blank
52. Numbness or tingling in parts of your body
53. A lump in your throat
54. Feeling hopeless about the future
55. Trouble concentrating
56. Feeling weak in parts of your body
57. Feeling tense or keyed up
58. Heavy feelings in your arms or legs
59. Thoughts of death or dying
60. Overeating
61. Feeling uneasy when people are watching or talking about you
62. Having thoughts that are not your own
63. Having urges to beat, injure or harm someone
64. Awakening in the early morning
65. Having to repeat the same actions such as touching, counting, washing
66. Sleep that is restless or disturbed
67. Having urges to break or smash things
68. Having ideas or beliefs that others do not share
69. Feeling very self-conscious with others
70. Feeling uneasy in crowds, such as shopping or at a movie
71. Feeling everything is an effort
72. Spells of terror or panic
73. Feeling uncomfortable about eating or drinking in public
74. Getting into frequent arguments
75. Feeling nervous when you are left alone
76. Others not giving you proper credit for your achievements
77. Feeling lonely even when you are with people
78. Feeling so restless you couldn't sit still
79. Feelings of worthlessness
80. The feeling that something bad is going to happen to you
81. Shouting or throwing things
82. Feeling afraid you will faint in public
83. Feeling that people will take advantage of you if you let them
84. Having thoughts about sex that bother you a lot
85. The idea that you should be punished for your sins
86. Thoughts and images of a frightening nature
87. The idea that something serious is wrong with your body
88. Never feeling close to another person
89. Feelings of guilt
90. The idea that something is wrong with your mind
APPENDIX C, PROVISION OF SOCIAL RELATIONS (PSR) SCALE

NOW I WOULD LIKE TO KNOW SOMETHING ABOUT YOUR RELATIONSHIPS WITH OTHER PEOPLE. FOR EACH OF THE STATEMENTS I READ TO YOU PLEASE USE THE SCALE ON THIS CARD TO TELL ME THE NUMBER OF CATEGORY THAT BEST DESCRIBES YOUR EXPERIENCE.

1. When I am with my friends I feel completely able to relax and be myself. 
2. I share the same approach to life that many of my friends do. 
3. People who know me trust me and respect me. 
4. No matter what happens, I know that my family will always be there for me should I need them. 
5. When I want to go out and do things I know that many of my friends would enjoy doing these things with me. 
6. I have at least one friend that I could tell anything to. 
7. Sometimes I'm not sure if I can completely rely on my family. 
8. My family lets me know they think I am a worthwhile person. 
9. I feel very close to some of my friends. 
10. People in my family have confidence in me. 
11. People in my family provide me with help in finding solutions to my problems. 
12. People who know me think I am good at what I do. 
13. My friends would take time to talk over my problems, should I ever want to. 
14. I know my family will always stand by me. 
15. Even when I am with my friends I feel alone.

RESPONSE SCALE
1. very much like my experience.
2. much like my experience.
3. somewhat like my experience.
4. not very much like my experience.
5. not at all like my experience.
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