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A STATISTICAL ANALYSIS OF ALPHA-1 ANTITRYPSIN AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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A STATISTICAL ANALYSIS OF ALPHA-1 ANTITRYPSIN AND

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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CHAPTER I

INTRODUCTION AND REVIEW OF LITERATURE

New impetus has been added to the existing field of medical research with the discovery of a biochemical abnormality associated with certain types of lung disease. Laurell and Eriksson (1) were the first to report an association between a deficient proteinase inhibitor in human serum, alpha-1 antitrypsin, and degenerative pulmonary disease in 1963. Their observation of three patients among 1500 consecutive serum electrophoretic paper strips with no distinctly demarcated bands in the alpha-1 zone suggested this association and led to further analysis of the alpha-1 antitrypsin deficiency (AAD).

The pulmonary disease Laurell, Eriksson, and others have referred to in their research has been termed chronic obstructive pulmonary disease (COPD), which is a disorder characterized by a persistent or chronic obstruction to bronchial airflow and includes emphysema, chronic bronchitis, and asthma. Various authors have used similar expressions such as chronic obstructive lung disease (COLD),(2), emphysema-chronic bronchitis syndrome (3), obstructive ventilatory syndrome, and others; however, each of these terms describes a disorder having the basic char-

acteristic mentioned above. An excellent discussion of COPD in relation to definition, prevalence, etiology, etc., has been prepared by a committee of the Oregon Thoracic Society (4). In discussing the terminology this manual states:

> Varying interpretations of these clinical terms have led to confusion in the medical literature and to difficulties in the analysis of morbidity and mortality data. While pulmonary emphysema continues to be the most widely used clinical term, some suggest that the diagnosis of emphysema should be left to the pathologist, who can define it in terms of morbid anatomy.

Until 1958 no satisfactory definition of emphysema existed although the term was used extensively by both clinicians and pathologists.

The following definitions of emphysema, chronic bronchitis, and asthma are those set forth by the American Thoracic Society (5). Emphysema is formally defined anatomically as a condition of the lungs characterized by an increase beyond the normal in the size of the air spaces distal to the terminal bronchiole either from dilatation or from destruction of their walls. In comparison to this pathological definition various clinical, radiological, and physiological criteria have been formulated in an attempt to define emphysema with varying degrees of success (6 - 13). It is of interest that much of the modern knowledge of emphysema was established by Laennec in 1819 and is still used today. Rosenblatt (14) historically describes emphysema from its first written account in 1679 by Boneti up to and including the 19th century. A recent monograph by Farber and Wilson (15) discusses emphysema in detail. Chronic bronchitis is defined in clinical terms as a chronic or recurrent increase above the normal in the volume of bronchial mucous secretion sufficient to cause expectoration when this is not due to localized bronchopulmonary disease. Chronic or recurrent may be further defined as present

on most days during at least three months in each of two successive years. Asthma is defined as a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airway that changes in severity either spontaneously or as a result of therapy.

Patients with COPD may have both anatomical emphysema and chronic bronchitis, or may have either one or the other, or in some cases may have a chronic airway obstruction in the absence of both emphysema and chronic bronchitis; however, emphysema is the main contributor of deaths and disabilities and is the primary disorder to which AAD has been related. The present difficulty in separating COPD patients into either emphysematous or chronic bronchitic patients lies not only in the lack of distinctive definitions but also in the comparative symptomatology. Several signs and symptoms are characteristic of each disease entity, although a considerable overlap of these factors can occur in the early stages of disease.

Dyspnea, wheeze, shortness of breath, and cough are common compliants among patients with COPD as well as expectoration, experiences of acute respiratory infection, weight loss, and general weakness. These discomforts progressively worsen although patients frequently delay medical examination until after 40 years of age while experiencing respiratory incapacities much earlier. Kleinerman et al. (16) observed a considerable number of lesions in lungs of a supposedly nondiseased population aged 15 to 44, which again emphasizes the need for early detection and therapy. Physical findings are variable depending on the severity and progression of the disorder. A physiological abnormality consist-

ently present is the slowing of forced expiration; while normal breathing may not reveal this abnormality, it becomes more evident after a rapid expiration following a full inspiration. In a healthy individual there is usually a pause after each expiration before the beginning of the next inspiration; however, emphysematous patients do not or can not exhale the air from their lungs before the next inspiration begins.

Spirometry has been instrumental in determining the diagnosis and prognosis of patients with COPD. The assessment of the amount of ventilatory impairment due to slowed expiratory flow can be evaluated through several spirometric variables. The forced expiratory volume in one second ($FEV_{1.0}$) is the amount of expired air measured in liters after a full inspiration, and the ratio of $FEV_{1.0}$ to the forced vital capacity (FVC) is an indicator of expiratory flow. The lower this ratio is the greater difficulty an individual has in forcing air from his lungs. A ratio less than 70% is generally diagnostic of an obstructive disorder, but by itself this variable does not accurately distinguish diseased from nondiseased individuals. The $FEV_{1.0}$ is also one of the most useful measurements in assessing the progression of obstructive lung disease (17). Other measurements of ventilatory flow including the midexpiratory flow rate ($FEF_{.25-.75}$), $FEV_{0.5}/FVC$, and the $FEV_{1.0}$ expressed as a percent of the predicted value have been associated with airway obstruction. Measurements by Kory et al. (18) among normal subjects provide predicted spirometry values based on an individual's age, sex, and height.

Radiology is also helpful in revealing a variety of abnormalities; however, as with specific spirometry variables, the chest x-ray should not be considered a final criteria in diagnosing COPD. Studies

have demonstrated that radiographic information alone is not sufficient to warrant a diagnosis of COPD (19-21). Also inter-observer error among experienced clinicians and radiologist is a well known phenomenon.

Other clinical features or techniques of assessing COPD in patients include percussion, a decreased diaphragmatic excursion, a distortion of the chest cavity, blood gas and acid-base determinations, and electrocardiography. These assessments may be of value in diagnosing individual patients, but they are not readily applicable in studying large populations.

All these aspects of COPD mentioned above point out the apparent difficulty in accurately distinguishing COPD from other disorders and in distinguishing emphysema, chronic bronchitis, and asthma from each other. Diagnoses based on one or two variables can be misleading because of the overlap of symptomatology among these disease entities. Studies (10,13, 19,22) using autopsy information have investigated COPD in an attempt to clarify which variables are most relevant in making accurate diagnoses. Radiology, spirometry, and clinical evaluations were obtained on COPD patients and then these factors were correlated with the autopsy data. The analyses generally consisted of multiple comparisons, although Burrow et al. (22) used stepwise multiple regression in order to predict an emphysema score.

The importance of investigating COPD, regardless of the perplexities of definition and symptomatology, is emphasized by the reported increase in prevalence of this disorder. According to the manual prepared by the Oregon Thoracic Society (4), "COPD is by far the commonest chronic pulmonary disease. Its prevalence and death rate like those of broncho-

genic carcinoma have increased spectacularly in recent years." Table 1 shows the mortality rates for emphysema, chronic bronchitis, and asthma in comparison to malignant neoplasms of the respiratory system from 1961 to 1971. All rates and figures are from the Vital Statistics of the United States and the Monthly Vital Statistics Reports (23,24). The rates from 1961 to 1969 are based on final figures while those of 1970 and 1971 are based on a 10% sample of deaths. Whether the mortality rates are leveling off as the estimates of 1970 and 1971 indicate or will continue to increase can only be determined in later years. Emphysema has only been reported as a separate cause of death since 1948 and the mortality rate has increased sharply since then. Currently, emphysema is the 10th leading cause of reported deaths in the United States. The mortality rates of the subclassifications of COPD reveal a slight increase for chronic bronchitis, a decrease for asthma, and a very striking increase for emphysema. In comparison to malignant neoplasms of the respiratory system, the mortality rates for emphysema from 1961 to 1969 have increased by a greater percentage. The mortality rates by sex and race for the year 1968 are given in Table 2. Males have much higher mortality rates than females, and the white population has higher mortality rates than the nonwhite population. The Metropolitan Life Insurance Company has made similar observations in their Statistical Bulletin on data collected through claims in the company (25).

Another means of justifying the increased concern of COPD can be obtained through the Office of Research and Statistics of the Social Security Administration (26). Emphysema ranks second next to arteriosclerotic heart disease among workers for whom a period of disability was al-

TABLE 1

MORTALITY RATES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE
AND MALIGNANT NEOPLASMS OF THE RESPIRATORY SYSTEM
UNITED STATES, 1961 - 1971

Cause of Death	1961	1962	1963	1964	1965	1966	1967	1968	1968	1970	1971
Emphysema, Bronchitis, and Asthma ISC (490-493)[a]	9.9[b]	11.2	13.0	12.9	14.4	15.2	15.3	16.6	15.4	14.9	14.5
Chronic and Unqualified Bronchitis ISC (490-491)	1.7	1.9	2.3	2.3	2.5	2.6	2.7	3.1	2.9	2.7	2.6
Emphysema ISC (492)	5.6	6.7	8.0	8.3	9.6	10.3	10.6	12.1	11.4	11.1	10.8
Asthma ISC (493)	2.7	2.6	2.7	2.3	2.3	2.2	2.1	1.3	1.2	1.1	1.0
Malignant Neoplasms of the Respiratory System ISC (160-163)	23.1	24.0	24.9	25.7	26.8	28.0	29.4	31.8	32.7	33.9	34.6

[a]Numbers after causes of death are category numbers of the Eighth Revision, International Classification of Diseases, Adapted 1965.

[b]Rates per 100,000 estimated population

TABLE 2

MORTALITY RATES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE
AND MALIGNANT NEOPLASMS OF THE RESPIRATORY SYSTEM
BY SEX AND RACE, UNITED STATES, 1968

Cause of Death	Total	Male	Female	White Male	White Female	Nonwhite Male	Nonwhite Female
Emphysema, Bronchitis, and Asthma ISC (490-493)[a]	16.6[b]	26.9	6.7	28.6	6.9	14.7	5.3
Chronic and Unqualified Bronchitis ISC (490-491)	3.1	4.7	1.6	5.0	1.7	2.8	1.0
Emphysema ISC (492)	12.1	20.9	3.7	22.6	4.0	9.1	1.5
Asthma ISC (493)	1.3	1.3	1.3	1.1	1.2	2.8	2.8
Malignant Neoplasms of the Respiratory System ISC (160-163)	31.8	53.5	11.1	54.7	11.4	44.3	8.4

[a]Numbers after causes of death are category numbers of the Eighth Revision, International Classification of Diseases, Adapted 1965

[b]Rates per 100,000 estimated population

lowed in 1965. When classified by sex, emphysema still ranked 2nd among males and 8th among females. Also for workers aged 50 and above emphysema ranked 2nd, while in the 35-49 year age group it ranked 5th.

Thus by using mortality and disability data as indicators of prevalence, COPD is indeed of vital concern to the health of this nation. The increase in mortality due to COPD is impressive even with an increased awareness of the disorder among physicians and patients, with a change in the classification of the disease, and with altered reporting practices. In comparing the physician's information of death certificates with what they answered several months later on a questionnaire, Markush (27) suggests that vital statistics based on death certificate information may seriously underestimate the contribution of this disease towards total mortality in the United States. In constrast, Rosenblatt (28) refutes this alarming concern as a statistical illusion of an emphysema epidemic.

With the discovery of the AAD and with the increased concern of environmental pollutants and smoking, perhaps some additional knowledge can be formulated in an attempt to solve the unknown etiologic bases of COPD. Since Laurell and Eriksson's initial publication, several researchers using comparative techniques of assay including enzymatic inhibition tests, immunodiffusion or immunoelectrophoresis, and crossed antigen-antibody electrophoresis have documented an association between AAD and COPD, particularly emphysema.

Eriksson (29), in studying 14 members of one family, found 3 levels of alpha-1 antitrypsin concentration, designated as low, intermediate, and normal, and suggested a recessive type of heredity. The low and intermediate levels have been expressed as homozygous and heterozygous

states. Through family studies and an extensive hospital screening program, Eriksson (30) identified 33 homozygous deficient patients. Of these 17 males and 16 females, 15 males and 8 females had COPD. Six of the remaining 10 had not reached 40 years of age and could possibly develop lung disease later in life. Eleven of the 23 with COPD gave a history of chronic cough and repeated respiratory tract infections, before the onset of dyspnea. Dyspnea was the primary symptom in nine of the patients. All had ventilatory impairment. Eriksson discusses in detail the important developments in this area of research, and in a later publication (31) he reviews his studies and conclusions. Other authors (32,33) have also summarized the developments related to this topic.

In a group of patients with COLD beginning before age 40, Hepper et al. (2) found 5 homozygotes and 1 heterozygote among 14 males. They also reported 2 homozygotes and 3 heterozygotes in a group of COLD patients with a familial history of emphysema. In a familial study involving 93 members of six families and three additional persons, Talamo et al. (34) associated obstructive pulmonary disease with AAD. Of the 149 COPD patients studied by Erkstam et al.(11), five were homozygous deficient for alpha-1 antitrypsin. This group included chronic bronchitis and bronchiectasis as well as emphysema patients distinguished by histories, ventilatory capacities, and radiological sign of hyperinflation. Hunter et al. (35) discussed an interesting familial study of two deceased brothers who died of chronic pulmonary insufficiency in their thirties. Antitryptic levels for the family indicated two of the children of one brother were heterozygous while his wife and third child were normal. Seven individuals with low alpha-1 antitrypsin levels combined with clin-

ical and physiological characteristics sufficient to warrant emphysema were studied by Guenter et al. (36). Of these seven, two were asymptomatic while four had developed symptoms prior to age 40 and one after age 40. Lieberman (37) reported 7 homozygotes and 10 heterozygotes among a group of 66 emphysematous patients. Makino (38) observed 10 patients among 11 homozygotes who had COLD with exertional dyspnea as the prime symptom. Some also had symptoms of wheeze and sputum production, and five were misclassified as asthma patients. Similarly, Townley et al. (39) described the physiological characteristics of 15 alpha-1 antitrypsin deficient members of one family of which 5 had severe obstructive emphysema. Thus, by comparing the results of these studies, an association between low levels of alpha-1 antitrypsin and COPD or in particular pulmonary emphysema can readily be seen.

The association between pulmonary disease and the heterozygous alpha-1 antitrypsin deficiency or the intermediate level is not as well documented as the low levels. The confirmation of such an association would be of considerable medical significance since there are necessarily more heterozygotes than homozygotes in a population.

Several authors have reported an association of this type (37, 40 - 44), although other investigators have reported opposite findings (30, 45 - 47). Lieberman et al. (40) discussed the prevalence of AAD among various groups of people ranging from industrial workers to COLD patients. The prevalence of intermediate alpha-1 antitrypsin was 5% among aircraft workers (13 heterozygotes out of 278 employees) and the rate was 24.6% among the COLD patients. They also reported 17 patients with intermediate levels out of 400 acutely and chronically ill patients

without pulmonary disease (41). The authors concluded from these studies that heterozygosity predisposes to COPD. Kueppers et al. (42) reported 5 homozygotes and 25 heterozygotes for the deficient gene in a group of 103 patients with obstructive lung disease compared to only 14 among a control group of 100 subjects with a mean age of 36 and only 8 among a control group of 88 subjects with a mean age of 80 years. Similarly, Smith et al. (43) and Fallat et al. (44) describe their observations relating intermediate alpha-1 antitrypsin levels to COPD.

Eriksson (30) found no increased incidence of lung disease among relatives who were heterozygous or normal for alpha-1 antitrypsin. Of the 110 family members studied only one of 64 heterozygotes had pulmonary disease, but pulmonary function tests or chest x-rays were not performed on these subjects. Using the same serological techniques as Eriksson, Welch et al. (45) reported 17 subjects with intermediate levels in a group of 146 consecutive chest patients. This frequency was not significantly different than 3 intermediates out of 51 seen in a blood donor group. Similarly, Larsen et al. (46) observed no association between intermediate levels of alpha-1 antitrypsin and COPD in finding 13 heterozygotes out of 163 in a group of COPD patients compared to finding 18 heterozygotes out of 118 in a control group. In a preliminary report of a prospective study and in a study of obligate genetic heterozygotes, Guenter et al. (47) have not detected any relationship between spirometric abnormalities and intermediate serum levels of alpha-1 antitrypsin. Resnick et al. (48) were also unable to demonstrate an association between intermediate levels and symptomatology related to COPD.

In all these publications, attention should be given to the sam-

ple sizes and the particular groups of subjects involved before arriving at any overall conclusions. Certainly, prevalence rates for a particular group do not reflect the prevalence rate for the general population as a whole. Also, multiple testing and small sample sizes can lead to invalid conclusions. Another problem unique to these studies is the difficulty in classifying an individual as having or not having a particular disease and in distinguishing emphysema, chronic bronchitis, and chronic airway obstruction. Arbitrary standards of disease must be established in diagnosing COPD from clinical findings. These criteria have varied in several studies because of the populations involved and with the specific objectives of each study; nevertheless, aspects of medical history, spirometry, and radiology have sufficiently justified the diagnosis of COPD (11,36).

In this paper criteria based on the information assembled through respiratory symptom questionnaires, spirometry, and radiology was analyzed in relation to the association of alpha-1 antitrypsin and chronic obstructive pulmonary disease.

CHAPTER II

DESCRIPTION OF THE RESPIRATORY STUDY

The Department of Medicine in conjunction with the Department of Biostatistics and Epidemiology of the University of Oklahoma Health Sciences Center conducted an epidemiologic survey of respiratory disease in Seminole County, Oklahoma in 1968 - 1969. This survey formulated the basis of a longitudinal study entitled the Natural History of Chronic Bronchitis and Emphysema and was supported by Grant HL-13667-07 of the National Heart and Lung Institute.

The objectives of this study are to evaluate the role of racial factors, alpha-1 antitrypsin, and pulmonary infections in the development of chronic obstructive pulmonary disease (COPD) over an extended period of time. The same subjects that participated in the 1968 - 1969 study were evaluated again in 1971 - 1972 in order to accomplish these objectives.

Seminole County is located approximately 60 miles east of Oklahoma City in a predominantly rural environment. Both agriculture and the petroleum industry are major sources of employment for this area. For this study the county was divided into two geographic areas based on the accessibility and convenience of the two branches of the Seminole County Health Department. The sample living in the eastern area of the county

was scheduled to participate in the study during December, 1968 in Wewoka, Oklahoma; similarly, the selected sample living in the western area of the county was scheduled during May, 1969 in Seminole, Oklahoma. In both of these localities the facilities of the County Health Department and a mobile unit provided by the Oklahoma State Health Department were used.

A comprehensive sampling frame of the adult population of Seminole County was prepared from available public records such as telephone books, municipal and rural utility lists, voter registration lists, and other sources with the assistance of the Oklahoma Lung Association. This compilation of records was used in the selection of a random sample of adults; hereafter, the term sample is used in reference to this random selection. An initial sample of 1000 subjects was selected for the study and supplemented in consideration of those subjects no longer residing in the county.

Appointments were scheduled by mail and contacts made by telephone to answer questions concerning the purposes of the study and to encourage participation. Transportation was provided if necessary and an intensive publicity campaign was conducted through local news media to also encourage participation. The endorsement and cooperation of the County Health Society, State Heart Association, Oklahoma Lung Association, and the State Health Department were instrumental in the conduction of this study. A number of volunteers were also allowed to participate in the study to provide public relations support.

From every subject participating in the study a chest roentgenogram, a spirogram, a venous blood specimen, and a completed questionnaire similar to the British Medical Research Council questionnaire regarding

pulmonary symptomatology and appropriate history were obtained.

Specifically the questionnaire (Form I, Appendix) was designed to obtain pertinent information regarding medical history, occupational exposure to respiratory irritants, smoking history, familial history of pulmonary disease, and symptomatology related to COPD. All responses on this questionnaire had been numerically coded for computer processing prior to the operation of the clinic. For each question, the appropriate response was circled and the numerical code recorded in the right hand margin. The respiratory questionnaire was administered by interviewers trained by the Department of Biostatistics and Epidemiology.

The venous blood specimen was analyzed for antitryptic activity by the trypsin inhibitory capacity (TIC) method as modified by Eriksson (30) and by immunodiffusion. This analysis was performed by biochemists with special experience in this procedure in the Pulmonary Laboratory of University in Oklahoma City. Quality control was monitored by analyzing known samples in each daily run. These known samples were also used in the designation of low, intermediate, and normal levels of TIC which were determined to be less than 0.33 mg/ml, 0.33 to 0.62 mg/ml, and greater than 0.62 mg/ml respectively.

Spirometry was performed on a Stead-Wells Spirometer with predicted values obtained from the data of Kory et al. (18). The forced expiratory volume in 0.5 and 1.0 seconds, the midexpiratory flow rate, and the forced vital capacity were recorded from the trial having the greatest forced vital capacity. A technician from the Pulmonary Function Laboratory was responsible for the collection of the spirometry data. Calculations of observed and predicted values and the corresponding ratios were

determined by the personnel of this laboratory.

Chest roentgenograms were taken by a technician employed by the State Health Department and interpreted by clinicians of the Department of Medicine. Intra-observer and inter-observer comparisons were made to validate the interpretations of the chest films. Evidence of COPD was indicated as present if hyperinflation or bullae were noted.

The TIC determinations, spirometry data, and chest roentgenogram interpretations were recorded on a separate form (Form II, Appendix) for each subject. This form was also designed for computer processing.

CHAPTER III

METHODS OF ANALYSIS

The data collected on Forms I and II were combined and incorporated into a data base utilizing a computer system, General Information and Processing System (GIPSY®), which greatly facilitates retrieving relevant information. This data base was thoroughly checked for completeness and accuracy by the use of this computer system. Any errors of omission or inconsistencies in the responses of sequences of questions were corrected by searching the original sources of information.

The variables to be considered in the analysis of whether subjects with intermediate values of trypsin inhibitory capacity (TIC) are more susceptible to chronic obstructive pulmonary disease (COPD) than subjects with normal TIC values are indicated in Table 3. This table also indicates the terminology in reference to the basic sections of the respiratory questionnaire, spirometry and laboratory data, and the location of these variables by Form number and column and/or question number.

Univariate and multivariate statistics were used in the analyses of these data to describe the possible relationships between the different variables, to determine whether an association exists between intermediate TIC values and symptomatology of COPD, and to develop a model

TABLE 3

VARIABLES INCLUDED IN THE ANALYSIS

Variable and Terminology	Location By Column Question Number	
FORM I		
Sex	10	
Race	11	
Marriage	12	
Socio-economic Status	13	
Smoking History	17-30	1,2,3
Occupational Exposure	31-38	4
Morning Cough	40-43	5
Three Month Cough	44-45	6
Phlegm	46-53	7
Ease of Breathing	54	9
Wheeze	55-56	10
Periodic Wheeze	57-63	11
Recent Chest Illness	64-70	12
Heart Trouble	75-77	14
FORM II		
Age	13-14	
Forced Vital Capacity (FVC)	16-22	
Forced Expiratory Volume 0.5 Sec. ($FEV_{0.5}$)	23-29	
Forced Expiratory Volume 1.0 Sec. ($FEV_{1.0}$)	30-36	
Midexpiratory Flow Rate (FEF)	41-47	
Trypsin Inhibitory Capacity (TIC)	52-54	
Chest Roentgenography	59	

which would identify subjects suspected of having or developing COPD.

The variables relating to symptomatology of COPD are described to clarify their significance in relationship with each other and with the TIC values; for example, subjects with symptoms of morning cough or phlegm production should have on the average poorer spirometry values than subjects who do not have these symptoms, if these symptoms are necessarily associated with COPD. Similarly, subjects with low or intermediate levels of TIC were compared to subjects with normal values of TIC with respect to the presence or absence of these COPD symptoms.

Caution must be exercised in interpreting the multiplicity of results among these variables. As an example, if a significant difference was found between two groups for one of the spirometric variables, then significant differences will probably occur among other spirometric variables since they are dependent. Similarly, if morning cough is associated with x-ray evidence of COPD, then one may suspect phlegm production to also be associated because of the comparability of morning cough and phlegm production. Although the reported significance level is appropriate for each test, this form of multiple testing on related or dependent variables can produce more significant differences than in the case of testing independent variables.

Combinations of several variables were also investigated to define specific areas of interest such as in the identification of smokers or in the selection of subjects most likely to have COPD. Other comparisons between demographic characteristics of the sample and TIC values are also described.

The relationship between age and TIC values suggested a possible

linear or curvilinear association; therefore for each sex, the best fitting polynomial of low degree was found by the least squares method.

Finally, to find if some linear combination of variables could adequately discriminate between two selected groups of subjects and to verify if this discriminant criteria could serve as a future model for respiratory studies, the statistical methods of linear discriminant analysis were performed. Basically the technique of discriminant analysis searches for that linear combination of variables which will classify a subject as belonging to either one of two known groups better than any other linear combination of these variables. The two groups were determined by their TIC values, and the subjects in each of these groups were classified into either a high or low risk group based on the results of the linear discriminant function. Subjects with low or intermediate levels of TIC were in one group while subjects with normal values were in the second group. These two groups may be illustrated geometrically as two clusters of points in Euclidean k-space. The method of discriminant analysis projects these points onto a line so that the between sum of squares of the two projected groups is as large as possible relative to the within group sum of squares.

The best discriminant criteria derived by means of this method of analysis was then applied to a similar set of data obtained from different subjects in Muskogee County, Oklahoma during 1972 in order to predict its reproducibility. This second set of data was part of a larger data base that was collected in order to accomplish the objectives of the original Natural History of Chronic Bronchitis and Emphysema Grant of 1968 and to investigate further hypotheses concerning alpha-1 antitryp-

sin and chronic obstructive pulmonary disease. The data obtained was therefore comparable in the information obtained from the respiratory symptom questionnaire, in the techniques for obtaining spirometric results, and in the laboratory determinations of trypsin inhibitory capacity.

CHAPTER IV

RESULTS

The subjects of Seminole County, Oklahoma selected in the sample responded quite favorably to this epidemiologic study of chronic bronchitis and emphysema. A total of 796 subjects, 391 males and 405 females from a sample of approximately 1,000 subjects participated in the study during December, 1968 and May, 1969.

The data from the respiratory questionnaire, spirometry, TIC determination, and chest roentgenogram were assembled to form one record for each participant and formatted into a data base especially designed for computer retrieval. Some subjects had incomplete records in that certain aspects of the data were not obtained; however, subjects with incomplete records are relatively few in number. TIC values were determined on 767 of the 796 participants, but could not be determined on 13 male and 16 female subjects. Spirometry results were obtainable on 789 participants, but could not be performed by 4 male and 3 female subjects. Finally, chest films of 30 participants, 16 male and 14 female subjects, were found to be inadequate for interpretation. The respiratory questionnaire for each participant's record is complete with respect to the variables indicated in Table 3 (p. 19) although quantifying responses such as duration, type of illness, and degree of symptomatology are in-

complete on a relatively few records. Tables 4-16 summarize, where appropriate, the responses given by the participants on the respiratory questionnaire by sex for the total number of participants, the number of participants with TIC determinations, and the number of participants with chest x-ray results. These data were used in the analysis of each variable and in combinations of several variables in relation to evidence of COPD and TIC values. Additional classifications of these figures are given under the appropriate subtitle headings.

Trypsin Inhibitory Capacity

The biochemical analysis of the blood specimens identified 3 low, 108 intermediate, and 656 normal TIC values according to the classification criteria established in University Hospital's Pulmonary Laboratory. Figure 1 shows the distribution of the TIC values which had a mean value of 0.769 mg/ml and a standard deviation of 0.145 mg/ml. Figure 1 does not show the few extreme values below 0.35 mg/ml and greater than 1.15 mg/ml. For this study the 3 subjects with low TIC values (0.17, 0.23, and 0.23 mg/ml) were included in the analyses with subjects who had intermediate TIC values. With this inclusion, the prevalence rate of intermediate values is 14.47%. Hereafter, the term intermediate is in reference to all subjects whose TIC values are less than or equal to 0.62.

The association between TIC levels and symptoms of COPD is given for each variable in the following subsections.

Race

Table 4 shows the racial composition of the sample by sex with the mean age and TIC value for each group. There were no significant

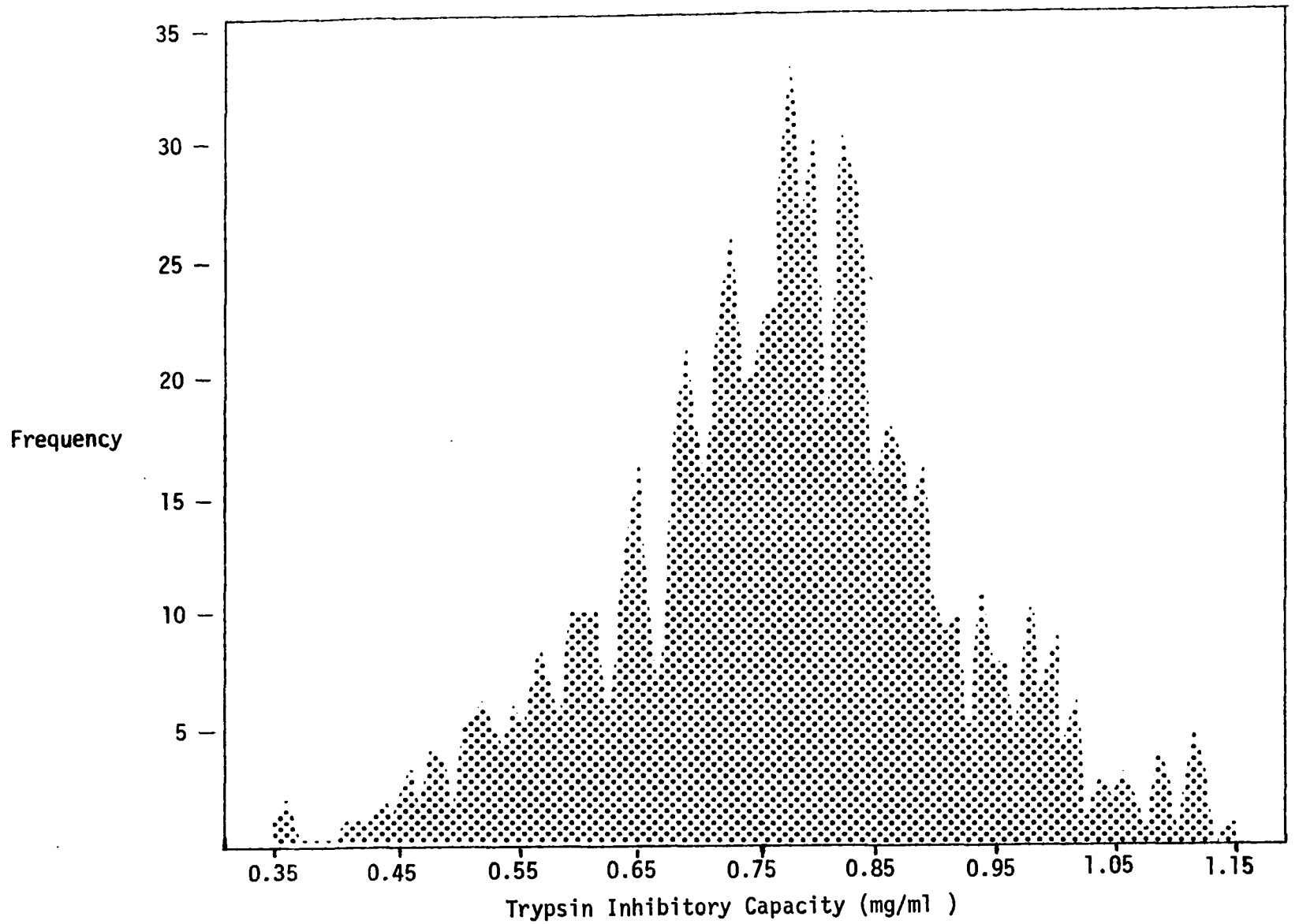

Figure 1 Distribution of Trypsin Inhibitory Capacity Results, Seminole County

TABLE 4

RACIAL COMPOSITION OF SAMPLE BY SEX WITH MEAN, RANGE, AND STANDARD DEVIATION STATISTICS ON AGE AND TIC

Race and Sex	Age			
	Number	Mean	Range	Standard Deviation
White Male	344	55.24	16-88	14.95
White Female	357	54.87	20-88	14.20
Negro Male	27	57.66	30-78	12.31
Negro Female	31	57.39	21-86	14.47
Indian Male	20	50.35	17-73	15.75
Indian Female	17	55.00	34-81	14.15
All Races Male	391	55.16	16-88	14.84
All Races Female	405	55.07	20-88	14.35
	TIC			
White Male	331	0.744	0.17-1.32	0.14
White Female	344	0.790	0.23-1.39	0.15
Negro Male	27	0.780	0.47-1.12	0.17
Negro Female	30	0.745	0.45-1.01	0.13
Indian Male	20	0.813	0.53-1.00	0.11
Indian Female	15	0.773	0.54-0.90	0.11
All Races Male	378	0.750	0.17-1.32	0.14
All Races Female	389	0.786	0.23-1.39	0.15

differences in the mean ages by race when male and female subjects were analyzed separately by the one way analysis of variance test with unequal sample sizes. Differences in TIC means for male and female subjects were also nonsignificant at the 5% level among the races.

These results are given merely to describe the data with respect to race; the small frequencies of nonwhite groups of subjects do not permit reliable generalizations among the races and consequently no differentiation among the races was performed in these analyses. It is interesting to note however that nonwhite male subjects had a higher TIC mean than white male subjects while the converse was indicated for female subjects.

The criteria for the classification of subjects by race, especially for Indian subjects, in studies of this type varies with the nature of the study itself and with an individual's self concept. These criteria have apparently caused some apprehension in the interpretation of data from Indian subjects. The 37 subjects of the Indian race in this study are primarily from the Seminole, Creek, Cherokee, and Choctaw tribes and genetically vary in degree from 1/16 to full blooded.

Sex

Figures 2 and 3 illustrate the distributions of TIC values for male and female subjects. The TIC distribution for female subjects appears to be shifted slightly to the right and had a significantly higher ($p < 0.001$) TIC mean than male subjects as indicated by the "t" test. When the distributions of TIC values for white male subjects (mean = 0.744 mg/ml) was compared with white female subjects (mean = 0.790 mg/ml), the difference in means was even greater. This significant differ-

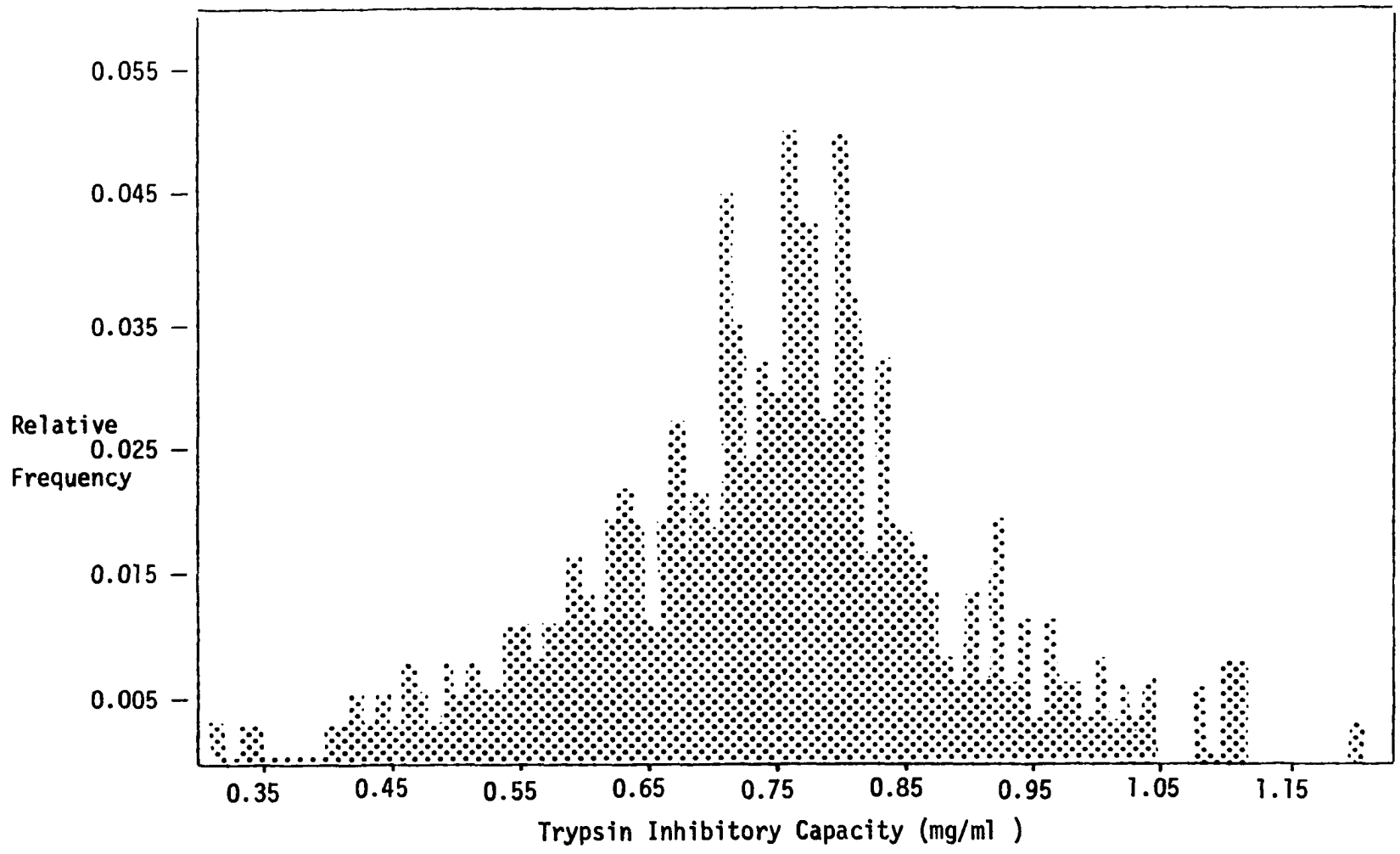

Figure 2 Distribution of Trypsin Inhibitory Capacity Results, Male Subjects

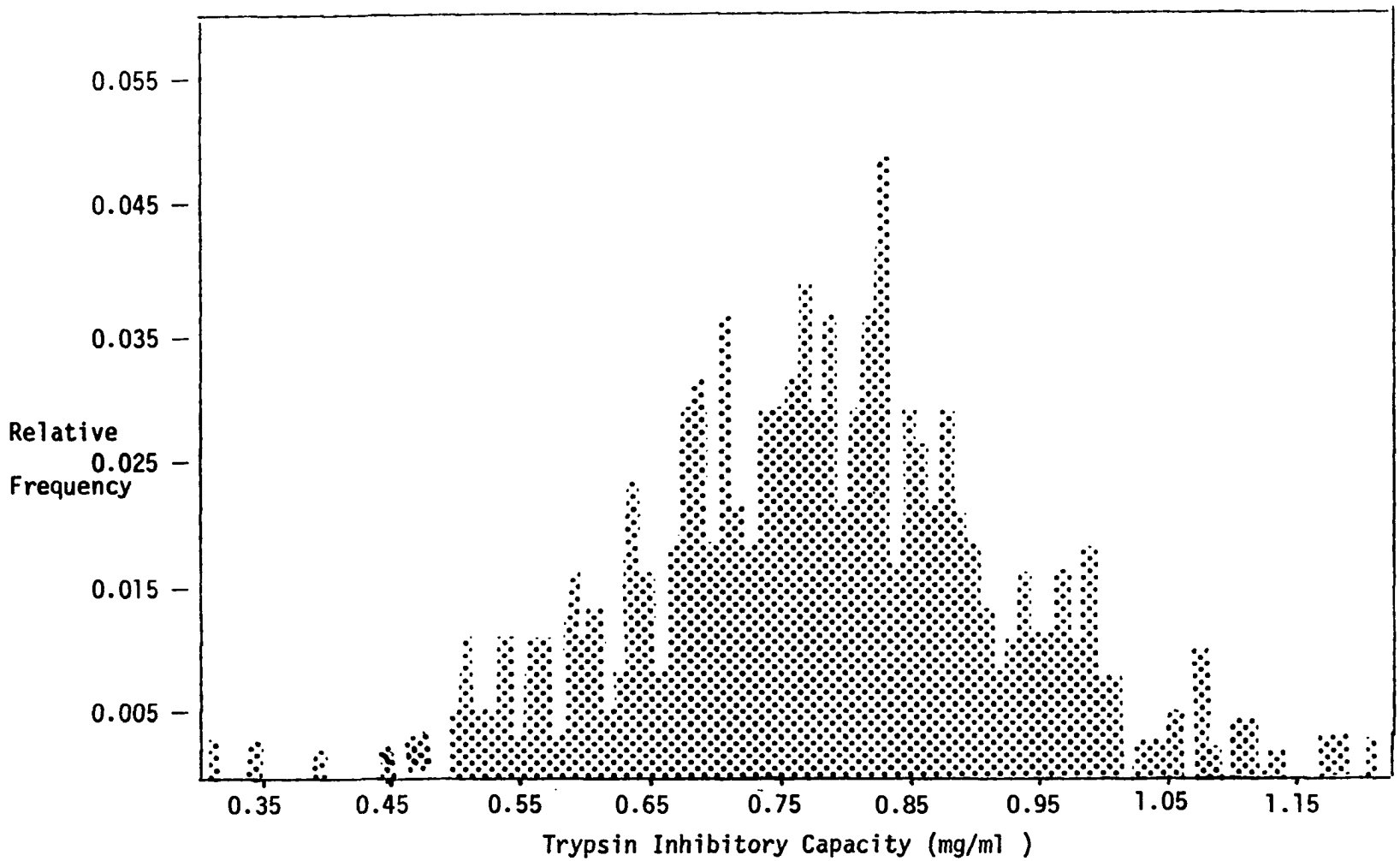

Figure 3 Distribution of Trypsin Inhibitory Capacity Results, Female Subjects

ence in TIC means for male and female subjects has been taken into account in subsequent descriptive and inferential analyses.

Age

A search was made to find a polynomial of low degree that would describe the relationship of age to TIC. The model used in this search can be written as

$$Y_j = B_0 + B_1X_j + B_2X_j^2 + B_3X_j^3 + B_4X_j^4 + E_j \qquad j = 1,2, \ldots, n_j$$

where Y_j is the j^{th} subject's TIC value and X_j is the j^{th} subject's age. Polynomials for male and female subjects were investigated and Table 5 shows the results of this search. Significance in this table implies that B_i ($i = 1, 2, 3, 4$) are different than zero and contribute to the model while nonsignificance implies the B_i are not different than zero.

For male subjects, B_2, B_3, and B_4 were not different than zero; therefore, the best linear polynomial to fit the data is:

$$Y = 0.75023 + 0.0016485(X - 55.21164)$$

Figure 4 shows this linear polynomial in comparison to the TIC means for each 5 year age group as indicated on the figure. The linear correlation coefficient between TIC values and age for male subjects was $R = 0.1689$ and R^2, which is a measure of the goodness of fit of the regression line, was only 0.0285. A second linear polynomial was calculated for male subjects 45 years of age and older, but R^2 for this regression line only increased to 0.36.

For female subjects, B_3 and B_4 were nonsignificant and the best quadratic polynomial, shown in Figure 5, to fit the data is:

$$Y = 0.78625 - 0.0106911(X - 54.92288) + 0.000085469(X^2 - 3224.7224)$$

TABLE 5

ANALYSIS OF VARIANCE FOR TIC VALUES AND AGE

Male

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F
Total	378	220.6877		
Mean	1	212.7600		
Linear Term (B_1)	1	0.2262	0.2262	11.34 *
Error for Linear Term	376	7.7015	0.0199	
Quadratic Term (B_2)	1	0.0458	0.0458	2.25 ns
Error for Quadratic Term	375	7.6556	0.0204	
Cubic Term (B_3)	1	0.0071	0.0071	0.35 ns
Error for Cubic Term	374	7.6485	0.0205	
Quartic Term (B_4)	1	0.0240	0.0240	1.18 ns
Error for Quartic Term	373	7.6246	0.0204	

Female

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F
Total	389	248.7533		
Mean	1	240.6681		
Linear Term (B_1)	1	0.1945	0.1945	9.31 *
Error for Linear Term	387	8.0852	0.0209	
Quadratic Term (B_2)	1	0.1780	0.1780	8.68 *
Error for Quadratic Term	386	7.9073	0.0205	
Cubic Term (B_3)	1	0.0643	0.0643	3.11 ns
Error for Cubic Term	385	7.9430	0.0206	
Quartic Term (B_4)	1	0.0088	0.0088	0.43 ns
Error for Quartic Term	384	7.8342	0.0204	

** significant at 0.005 level, $B_i \neq 0$
ns not significant at 0.05 level, $B_i = 0$

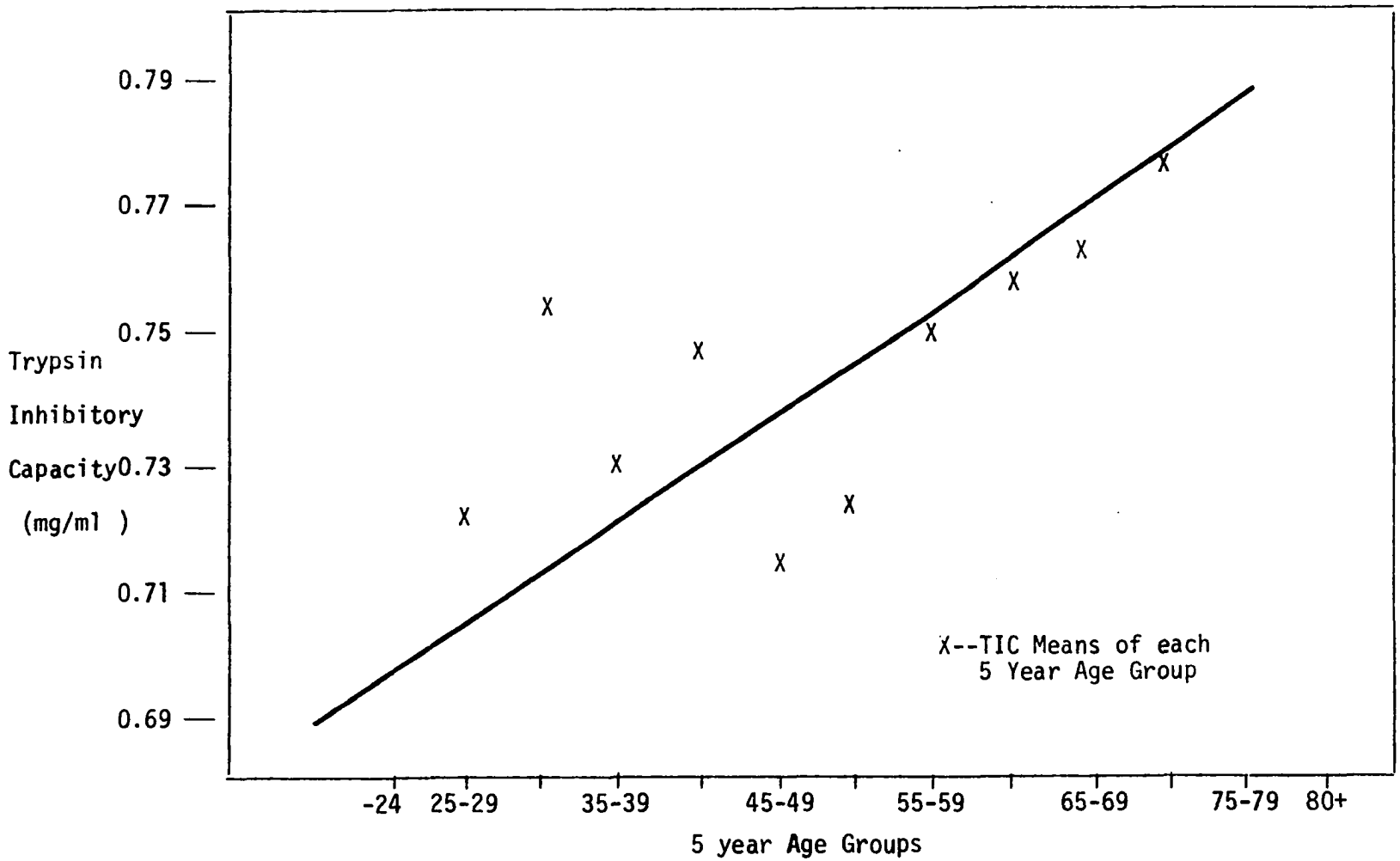

Figure 4 Graph Showing the Best Fitting Linear Polynomial in Comparison to the TIC Means of each 5 Year Age Group, Male Subjects

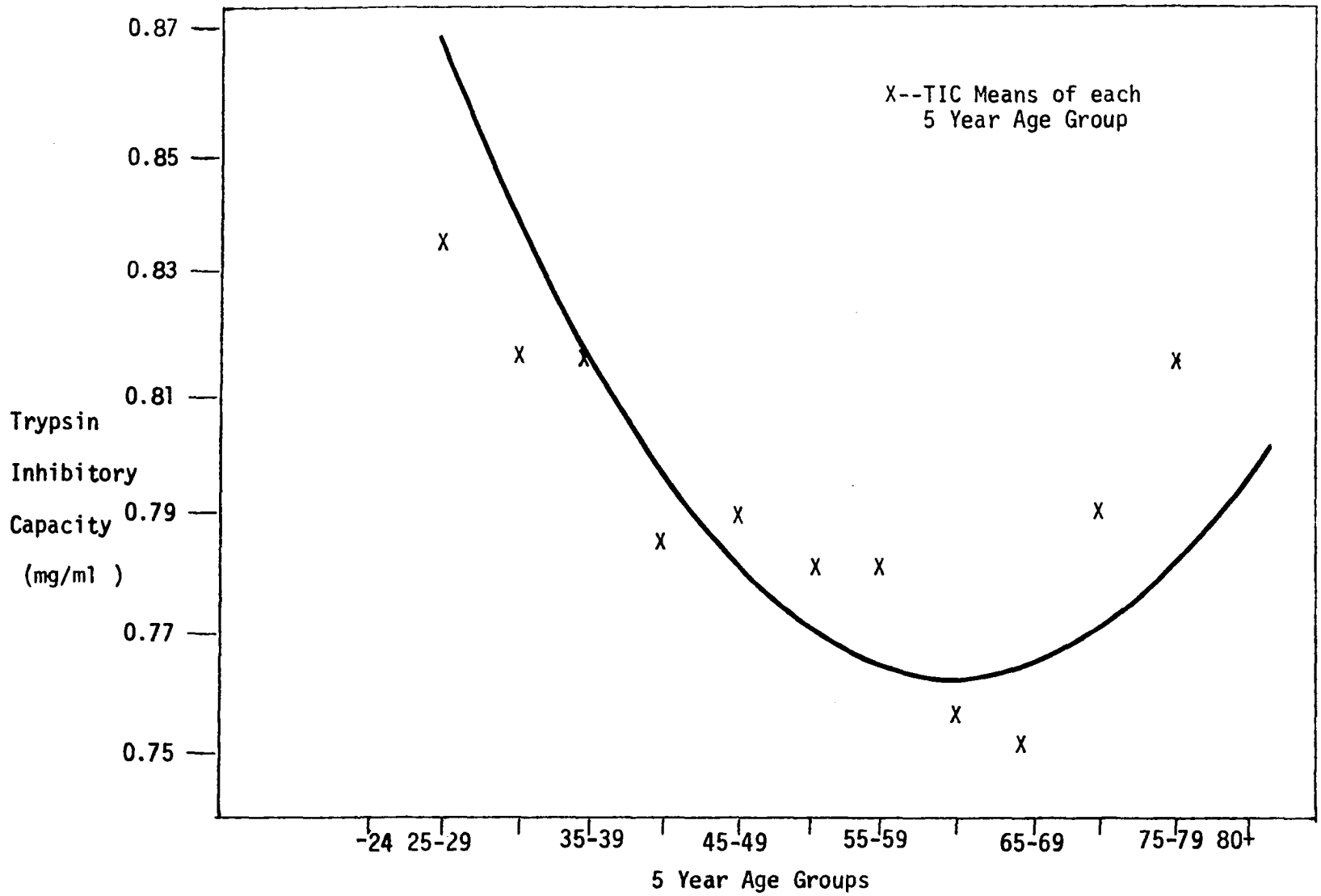

Figure 5 Graph Showing the Best Fitting Quadratic Polynomial in Comparison to the TIC Means of each 5 Year Age Group, Female Subjects

This quadratic is compared with the TIC means by 5 year age intervals and had a minimum at age 62.57. The multiple linear correlation coefficient was only 0.2121. The linear polynomial for female subjects had a slope of B_1 = -0.001549 which is approximately the same magnitude as that for male subjects but in the opposite direction.

Socio-Economic Status

A measure of an individual's socio-economic status was developed by Hollingshead (49) to meet the need of an objective, easily applicable procedure to estimate the positions individuals occupy in the status structure of our society. To determine the socio-economic status of an individual or of a household, the occupational role the head of household performs and the level of education he has attained is needed. These two factors are numerically coded, weighted, and combined to yield a score ranging from 11 to 77. This range is further classified into 5 intervals designated as types I through V. Type I represents the more affluent population with more formal education and prestigeous skills while type V represents that portion of the population with minimal education and generally unskilled. Table 6 shows the distribution of the socio-economic status for the head of household of each participant and also for each participant by intermediate and normal levels of TIC. The same criteria were used in classifying the participant and the head of household of that participant. This is a modification or addition to the procedures given by Hollingshead.

The Chi-square test was used to compare distributions of socio-economic status of subjects with intermediate values to subjects with normal values of TIC. The results were significant ($p < 0.10$) for the com-

TABLE 6

CLASSIFICATION OF SUBJECTS BY HOLLINGSHEAD SOCIO-ECONOMIC STATUS WITH INTERMEDIATE AND NORMAL LEVELS OF TIC

Head of Household

		I	II	III	IV	V
TIC Levels	Intermediate	2	14	49	30	15
	Normal	6	40	286	213	111
	Total	8	54	335	243	126

Subject

		I	II	III	IV	V
TIC Levels	Intermediate	1	11	54	33	11
	Normal	3	29	271	254	99
	Total	4	40	325	287	110

parison among heads of households wth greater proportions of intermediate values in social classes I, II, and III than expected. A similar analysis among participants was also significant ($p < 0.025$). Types I and II were combined because of the small frequencies expected in the type I category. The comparison of observed frequencies to expected in this second analysis also showed greater proportions of intermediate values in social classes I and II combined, and III than expected. These observations also imply that participants or heads of households with types IV and V indexes of socio-economic status had more observed subjects with normal values of TIC than expected.

Marriage

Table 7 shows the distribution of marital status for intermediate and normal levels of TIC. No significant differences were noted between these distributions when tested by the Chi-square test.

TABLE 7

DISTRIBUTION OF INTERMEDIATE AND NORMAL TIC LEVELS WITH MARITAL STATUS

		Married	Single	Widowed	Divorced	Separated
TIC Levels	Intermediate	93	5	9	4	0
	Normal	512	23	96	24	1
	Total	605	28	105	28	1

The subjects' responses to the variables which follow are discussed in relation to intermediate and normal levels of TIC, spirometry results, and evidence of COPD as indicated by chest roentgenography. To simplify the discussion pertaining to spirometric indications of COPD, the mean $FEV_{1.0}$, $FEV_{0.5}/FVC$, $FEV_{1.0}/FVC$, FEF, and the percent predicted for $FEV_{0.5}$, $FEV_{1.0}$, and FVC are collectively referred to as spirometric results. No distinction was made in determining which of these spirometric variables was the "best" indicator of a subject's ventilatory capacity. In most cases, the results for each of the spirometric variables were similar because of the dependency of the variables.

In the discussion to follow each variable can be referenced on Form I to obtain the exact wording of each question and other supporting quantifications.

Morning Cough

A total of 147 subjects (18.5%) answered yes to "Do you usually cough when you first get up in the morning"? Almost one-half of these subjects indicated having this symptom for more than 6 years. Out of the 64 male subjects in the intermediate TIC level, 15 (23.4%) indicated the presence of a morning cough in comparison to 81 (25.8%) of the 314 male subjects with normal TIC values. Out of the 47 female subjects in the intermediate TIC level, 4 (8.5%) indicated the presence of a morning cough compared to 41 (12.0%) of the 342 female subjects in the normal TIC level. Both 2x2 distributions as given in Table 8 showed no significant difference in the frequencies of responses to morning cough and TIC levels.

A significantly higher proportion (100/391 = 25.6%), ($p < 0.005$),

TABLE 8

DISTRIBUTION OF RESPONSES TO MORNING COUGH WITH INTERMEDIATE AND NORMAL LEVELS OF TIC AND WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

	Morning Cough							
	Male				Female			
TIC Levels	Yes	No	Total	% Yes	Yes	No	Total	% Yes
Intermediate	15	49	64	23.4	4	43	47	8.5
Normal	81	233	314	25.8	41	301	342	12.0
Total	96	282	378	25.4	45	344	389	11.6
X-ray Evidence of COPD	Yes	No	Total		Yes	No	Total	
Present	17	54	71		20	83	103	
Absent	77	227	304		25	263	288	
Total	94	281	375		45	346	391	
% Present	18.1	19.2	18.9		44.4	24.0	26.3	
Total Responses[a]	100	291	391		47	358	405	

[a]Totals are not the same since some TIC and x-ray results were not available.

of male subjects indicated a presence of morning cough than the corresponding proportion (47/405 = 11.6%) for female subjects. For subjects completing the spirometry portion of the study, 97 male and 47 female subjects with morning cough had significantly lower mean spirometry results than 290 male and 355 female subjects with no morning cough when tested separately by the "t" test.

The 2x2 frequency distributions of responses to morning cough with chest x-ray evidence of COPD was nonsignificant for male subjects, but was significant ($p < 0.01$) for female subjects. Twenty female subjects (44.4%) answered yes compared to 83 (24.0%) who answered no to the presence of morning cough and had chest x-ray evidence of COPD.

The mean TIC value both for male and female subjects was higher, but not significantly, for those answering yes to the presence of morning cough compared to the subjects answering no.

Three Month Cough

The presence of a cough for at least three months of the year was indicated by 99 subjects (12.4%) and was present in one-half of these subjects for at least six years. Table 9 shows the distribution of responses to this symptom of COPD. Ten male subjects (15.6%) with intermediate values of TIC had a cough for three months or more during the year compared to 52 male subjects (16.6%) with normal TIC values. Two female subjects (4.2%) with intermediate values indicated the presence of a cough for three months or more during the year compared to 30 female subjects (8.8%) with normal TIC values. The Chi-square test showed no significant differences in the distribution of responses for three month cough with intermediate and normal levels of TIC for both male and female

TABLE 9

DISTRIBUTION OF RESPONSES TO THREE MONTH COUGH WITH INTERMEDIATE AND NORMAL LEVELS OF TIC AND WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

	Three Month Cough							
	Male				Female			
TIC Levels	Yes	No	Total	% Yes	Yes	No	Total	% Yes
Intermediate	10	54	64	15.6	2	45	47	4.2
Normal	52	262	314	16.6	30	312	342	8.8
Total	62	326	378	16.4	32	357	389	8.2
X-ray Evidence of COPD	Yes	No	Total		Yes	No	Total	
Present	15	56	71		15	88	103	
Absent	48	256	304		18	270	288	
Total	63	312	375		33	358	391	
% Present	23.8	17.9	18.9		45.5	24.5	26.3	
Total Responses[a]	65	326	391		34	371	405	

[a]Totals are not the same since some TIC and x-ray results were not available.

subjects.

The proportion of male subjects (65/391 = 16.6%) that indicated a presence of cough for at least three months of the year was significantly higher ($p < 0.005$) than the corresponding proportion (34/405 = 8.3%) for female subjects when tested by the Chi-square test.

Both male and female subjects having cough for at least 3 months during the year had significantly lower mean spirometry values than those answering no to this symptom of COPD.

Male subjects with a cough for three months or more during the year showed no significantly greater presence of chest x-ray evidence of COPD than male subjects not having a three month cough; however, the 2x2 frequency distribution of three month cough responses with the presence or absence of chest x-ray evidence of COPD was significant ($p < 0.025$) for female subjects. Fifteen out of 33 (45.5%) female subjects had chest x-ray evidence of COPD compared to 88 out of 358 (24.5%) who did not.

The mean TIC value for male and female subjects who answered yes was higher, but not significantly, than the mean TIC value for those who answered no to having a cough for three months or more during the year.

Phlegm

The expectoration of phlegm beyond the normal for three months or more during the year for at least two successive years is the clinical definition of chronic bronchitis. The response to "Do you usually cough up phlegm from your chest?" and the duration of this experience are an integral part of the clinical definition of chronic bronchitis.

A total of 185 subjects indicated having phlegm produced from their chest; 34 subjects had this symptom of COPD less than one year, 76

subjects had this symptom 1 to 5 years, 30 subjects had this symptom 6 to 10 years, and 45 subjects had this symptom for over 11 years duration. Out of the 151 subjects with phlegm production for more than 1 year, only 25 (16.5%) indicated having bronchitis on questions 12 or 13, which pertain to experiencing chest illnesses within the past three years or prior to three years ago. With more than 6 years duration of phlegm production 16 (21.3%) indicated having bronchitis, and for the 45 subjects with more than 11 years duration, 14 (31.1%) mentioned having bronchitis. Similarly out of the 33 subjects mentioning bronchitis on question 12, 10 (30.3%) had phlegm production and 20 subjects out of 61 (32.8%) indicating bronchitis on question 13 had phlegm production. Only two subjects indicated having bronchitis on both questions 12 and 13.

Out of the 64 male subjects with intermediate TIC values, 15 (23.4%) had phlegm production compared to 97 (30.8%) of the 314 male subjects with normal TIC values. Similarly 9 (19.1%) of the 47 female subjects with intermediate TIC values had phlegm production compared to 57 (16.7%) of the 342 female subjects with normal TIC values. Neither of these 2x2 frequency distributions of responses with intermediate and normal levels of TIC showed any significant differences when examined by the Chi-square test. Table 10 shows these frequencies.

The 2x2 frequency distribution of responses to phlegm production with the presence or absence of chest x-ray evidence of COPD showed no significant difference for male subjects although the proportion of male subjects with phlegm production and the presence of chest x-ray evidence of COPD was greater than the proportion of male subjects not having this symptom and the presence of chest x-ray evidence of COPD (22.5% vs 17.4%).

TABLE 10

DISTRIBUTION OF RESPONSES TO PHLEGM WITH INTERMEDIATE AND NORMAL LEVELS OF TIC AND WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

	Phlegm							
	Male				Female			
TIC Levels	Yes	No	Total	% Yes	Yes	No	Total	% Yes
Intermediate	15	49	64	23.4	9	38	47	19.1
Normal	97	217	314	30.8	57	285	342	16.7
Total	112	266	378	29.6	66	323	389	17.0
X-ray Evidence of COPD	Yes	No	Total		Yes	No	Total	
Present	25	46	71		30	73	103	
Absent	86	218	304		38	250	288	
Total	111	265	375		68	323	391	
% Present	22.5	17.4	18.9		44.1	22.6	26.3	
Total Responses[a]	116	275	391		69	336	405	

[a]Totals are not the same since some TIC and x-ray results were not available.

The corresponding 2x2 frequency distribution for female subjects was significantly different ($p < 0.005$). A higher proportion of female subjects with phlegm had x-ray evidence of COPD than female subjects not having this symptom (44.1% vs 22.6%).

The proportion (116/391 = 29.6%) of male subjects indicating phlegm was significantly higher ($p < 0.005$) than the corresponding proportion (69/405 = 17.0%).

The 115 male subjects producing phlegm had significantly lower mean spirometry values than the 272 male subjects not having this symptom. Similarly, 69 female subjects having this symptom had significantly lower mean spirometry values than the 333 female subjects hot having phlegm produced from their chest.

The mean TIC value for both male and female subjects with phlegm production was higher, but not significantly higher, than subjects not having this experience. The "t" value for male subjects was 1.84.

Wheeze

The response to question 10, "Does your breathing ever sound wheezy or whistling?" was answered yes by 260 subjects. The response was further quantified as "only occasionally" by 187 subjects.

Twenty-one (32.8%) of the 64 male subjects with intermediate TIC values had wheeze compared to 120 (38.2%) of the 314 male subjects with normal TIC values. Fourteen (29.8%) of the 47 female subjects with intermediate TIC values answered yes to the presence of this symptom compared to 91 (26.6%) of the 342 female subjects with normal TIC values. Both the male and female 2x2 frequency distributions of responses to wheeze with intermediate and normal levels of TIC as shown in Table 11

TABLE 11

DISTRIBUTION OF RESPONSES TO WHEEZE WITH INTERMEDIATE AND NORMAL LEVELS OF TIC AND WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

	Wheeze							
	Male				Female			
TIC Levels	Yes	No	Total	% Yes	Yes	No	Total	% Yes
Intermediate	21	43	64	32.8	14	33	47	29.8
Normal	120	194	314	38.2	91	251	342	26.6
Total	141	237	378	37.3	105	284	389	26.9
X-ray Evidence of COPD	Yes	No	Total		Yes	No	Total	
Present	35	36	71		34	69	103	
Absent	110	194	304		75	213	288	
Total	145	230	375		109	282	391	
% Present	24.1	15.7	18.9		31.2	24.5	26.3	
Total Responses[a]	148	243	391		112	293	405	

[a]Totals are not the same since some TIC and x-ray results were not available.

were nonsignificant. However by using 0.49 mg/ml as the point of separation between intermediate and normal levels instead of 0.62 mg/ml, the frequency distribution of responses was significant ($p < 0.10$) for males.

The proportion (148/391 = 37.8%) of male subjects with symptoms of wheeze or whistling was significantly higher ($p < 0.005$) than the corresponding proportion (112/405 = 27.6%) of female subjects.

For those with spirometry results, 147 male subjects with symptoms of wheeze or whistling had significantly lower mean spirometry values than the 240 male subjects not having this symptom, and similarly 110 female subjects with wheeze had significantly lower mean spirometry values than the 292 female subjects not having this symptom.

The mean TIC value for both male and female subjects was higher, but not significantly higher, for subjects having symptoms of wheeze compared to subjects not indicating the presence of this symptom of COPD.

The 2x2 frequency distribution of responses to the presence of wheeze with the presence or absence of chest x-ray evidence of COPD was significantly different ($p < 0.10$) for male subjects but not for female subjects. A greater proportion (35/145 = 24.1%) of male subjects with wheeze had chest x-ray evidence of COPD than the proportion (36/230 = 15.7%) not having this symptom.

Periodic Wheeze

Periodic wheeze is the variable designated as the response given to question 11, "Have you ever had periodic attacks of wheezing or breathlessness?" and was present in 133 subjects. Of this number, 113 subjects stated having this symptom at times other than for chest colds. Similar results were obtained in comparing the 133 subjects to the 113 subjects

since they are essentially composed of the same subjects. Table 12 shows the distributions of responses for male and female subjects.

Fourteen male subjects (21.9%) in the intermediate TIC range of values had periodic symptoms of wheeze compared to 55 (17.5%) of the male subjects with normal TIC values. The 2x2 frequency distribution showed no significant differences; however, 8 of 18 (22.5%) male subjects had TIC values less than or equal to 0.49 mg/ml with symptoms of periodic wheeze compared to 61 of 360 (16.9%) male subjects with TIC values greater than 0.49 mg/ml. Using this criteria the resulting 2x2 frequency distribution of responses was significantly different ($p < 0.01$). Female subjects with intermediate as well as normal TIC values had the same proportion of responses indicating periodic attacks of wheezing.

The proportion (70/391 = 17.9%) of male subjects with periodic attacks of wheezing or breathlessness was not significantly different than the corresponding proportion (63/405 = 15.6%) of female subjects.

For subjects with complete spirometry results, 68 male subjects with periodic wheeze had significantly lower mean spirometry values than 319 male subjects not having this symptom. Similarly, 62 female subjects with periodic attacks of wheezing had significantly lower mean spirometry values than 340 female subjects not having this symptom.

The 2x2 frequency distribution of responses to periodic wheeze or breathlessness with the presence or absence of chest x-ray evidence of COPD was significantly different ($p < 0.01$) for male (30.4% vs 16.2%) but not for female subjects (32.8% vs 25.1%). The 70 males experiencing periodic wheeze had a significantly higher ($p < 0.01$) mean age than the 321 male subjects not having this symptom, and this would partially ex-

TABLE 12

DISTRIBUTION OF RESPONSES TO PERIODIC WHEEZE WITH INTERMEDIATE AND NORMAL LEVELS OF TIC AND WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

	Periodic Wheeze							
	Male				Female			
TIC Levels	Yes	No	Total	% Yes	Yes	No	Total	% Yes
Intermediate	14	50	64	21.9	7	40	47	14.9
Normal	55	259	314	17.5	51	291	342	14.9
Total	69	309	378	18.3	58	331	389	14.9
X-ray Evidence of COPD	Yes	No	Total		Yes	No	Total	
Present	21	50	71		20	83	103	
Absent	46	258	304		41	247	288	
Total	69	308	375		61	330	391	
% Present	30.4	16.2	18.9		32.8	25.1	26.3	
Total Responses[a]	70	321	391		63	342	405	

[a]Totals are not the same since some TIC and x-ray results were not available.

plain some of the differences between these two groups.

Both male and female subjects having periodic attacks of wheeze or breathlessness had higher mean TIC values, but not significantly higher than the subjects not having this symptom.

Occupational Exposure

Each subject was asked whether he or she had "ever worked for at least one year in a trade where you were exposed to a) dust or b) gases or fumes"? These responses are given in Table 13; unfortunately, a very high proportion of exposure to both dust and gases or fumes was classified as "other."

A significantly higher proportion ($p < 0.005$) of male subjects were employed in occupations exposing them to dust, gases, and fumes than female subjects (47.3% vs 15.8% and 39.0% vs 4.2%).

The spirometry results were not significantly different for male subjects working in dusty or gaseous occupations compared to male subjects not having such employment. Apparently occupational exposure to respiratory irritants did not affect the male subject's ventilatory capacity. The same was true for female subjects except for one ventilatory measurement; the $FEV_{1.0}/FVC$ was significantly lower ($p < 0.05$) for subjects working in dusty occupations compared to subjects not indicating such conditions. Other than this one "t" test, all other spirometry results for female subjects with either dusty or gaseous occupations were nonsignificant.

The 2x2 frequency distributions of responses to employment in dusty or gaseous occupations with the presence or absence of chest x-ray evidence of COPD were all nonsignificant except for male subjects

TABLE 13

DISTRIBUTION OF RESPONSES TO OCCUPATIONAL EXPOSURE WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

Dust Related Occupations

		Male			Female		
		Yes	No	Total	Yes	No	Total
X-ray Evidence of COPD	Present	42	29	71	14	89	103
	Absent	134	170	304	47	241	288
	Total	176	209	375	61	330	391
	% Present	23.8	14.6	18.9	23.0	26.9	26.3
	Total Responses[a]	185	206	391	64	341	405

Gas or Fume Related Occupations

		Male			Female		
		Yes	No	Total	Yes	No	Total
X-ray Evidence of COPD	Present	26	45	71	3	100	103
	Absent	119	185	304	13	275	288
	Total	145	230	375	16	375	391
	% Present	17.9	19.6	18.9	18.8	26.7	26.3
	Total Responses[a]	153	238	391	17	388	405

[a]Totals are not the same since some x-ray results were not available.

employed in dusty occupations. A significantly higher proportion ($p < 0.05$) of males with such employment had chest x-ray evidence of COPD than males not employed in dusty occupations (23.8% vs 14.6%).

The mean TIC value was higher, but not significantly higher, for male subjects employed in either dusty or gaseous occupations compared to subjects not indicating such employment. For female subjects, the mean TIC value was significantly lower ($p < 0.05$) for subjects working in dusty occupations compared to subjects not indicating this type of employment. No difference was noted in a similar comparison with gaseous occupations.

Chest Roentgenography

Table 14 shows the frequency distribution of chest x-ray evidence of COPD with intermediate and normal levels of TIC for male and female subjects. Neither 2x2 frequency distribution of results was significantly different. The comparisons of spirometry and TIC values among the subjects with unknown chest x-ray results indicated this group is not different than those subjects not having chest x-ray evidence of COPD.

The proportion (103/405 = 26.4%) of female subjects with chest x-ray evidence of COPD was significantly higher ($p < 0.025$) than the corresponding proportion (71/391 = 18.9%) of male subjects.

Results from spirometry showed significantly lower mean values for male subjects with chest x-ray evidence of COPD compared to subjects not having chest x-ray evidence of COPD: however, the average age of the first group with x-ray evidence was 9.1 years older than the group without x-ray evidence which would have an effect on spirometry results. Results for females were not conclusive; the mean differences for $FEV_{1.0}$,

TABLE 14

DISTRIBUTION OF THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD WITH INTERMEDIATE AND NORMAL LEVELS OF TIC BY SEX

Male

		Present	Absent	Unknown	Total
TIC Levels	Intermediate	14	48	2	64
	Normal	56	245	13	314
	Unknown	1	11	1	13
	Total	71	304	16	391

Female

		Present	Absent	Unknown	Total
TIC Levels	Intermediate	8	33	6	47
	Normal	90	244	8	342
	Unknown	5	11	0	16
	Total	103	288	14	405

and the percent of predicted results for FVC, $FEV_{0.5}$, and $FEV_{1.0}$ were not significant while the mean differences for $FEV_{0.5}$/FVC, $FEV_{1.0}$/FVC, and FEF were significant.

The mean TIC value for male subjects was significantly higher ($p < 0.05$) for subjects with chest x-ray evidence of COPD compared to subjects with no chest x-ray evidence of COPD. The same relationship between mean TIC values was true for female subjects although the results were not significantly different.

Heart Trouble

Approximately the same proportion of male and female subjects had some form of heart trouble as indicated on question 14. Female subjects with heart trouble were on the average 9.1 years older than female subjects with no heart trouble; similarly, the mean age difference for male subjects was 7.3 years. Approximately two-thirds of the subjects indicating some form or forms of heart trouble had a heart attack or had high blood pressure.

Both male and female subjects with a history of heart trouble had lower mean spirometry values than subjects not having any heart trouble; however, the age difference for both male and female subjects would account for some of the differences in the spirometry results.

The 2x2 frequency distributions of responses to heart trouble with the presence or absence of chest x-ray evidence of COPD was non-significant for both male and female subjects.

A retrieval of the data base was made to investigate the occurrence of COPD symptoms among male and female subjects with some form of heart trouble. Although these symptoms are characteristic of

COPD, they are also associated with other disease entities which may or may not occur in conjunction with pulmonary disease.

Of the 83 male subjects indicating a presence of heart trouble, 31 (37.4%) had morning cough, 21 (25.3%) had a cough for three months, 41 (49.4%) produced phlegm, 36 (43.4%) had an ease of breathing grade 2 or higher, 40 (48.2%) had a wheeze, 26 (31.3%) had a periodic wheeze, 19 (22.9%) had a recent chest illness, and 19 (22.9%) had chest x-ray evidence of COPD. In general the occurrence of these symptoms among the 83 male subjects with heart trouble accounted for approximately 30% of the symptoms indicated by all male subjects in the study.

A similar comparison among the 77 female subjects indicating heart trouble showed 11 (14.3%) had morning cough, 9 (11.7%) had a cough for three months, 17 (22.1%) produced phlegm, 35 (45.5%) had an ease of breathing grade 2 or higher, 32 (41.6%) had a wheeze, 18 (23.4%) had a periodic wheeze, 18 (23.4%) had a recent chest illness, and 19 (24.7%) had chest x-ray evidence of COPD. The occurrence of COPD symptoms among the 77 female subjects with heart trouble accounted for approximately 25% of the symptoms indicated by all the female subjects in the study.

The occurence of COPD symptoms in subjects with heart trouble is investigated in subsequent discriminant analysis.

Recent Chest Illness

Table 15 shows the frequency distribution of responses to question 12 on Form I, "During the last three years have you had a chest illness which kept you off work or at home indoors"? Twenty-four of the 137 subjects indicating a recent chest illness had this illness experience within the past month; however, spirometry and x-ray results showed

TABLE 15

DISTRIBUTION OF RESPONSES TO RECENT CHEST ILLNESS WITH INTERMEDIATE AND NORMAL LEVELS OF TIC AND WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

	Recent Chest Illness							
	Male				Female			
TIC Levels	Yes	No	Total	% Yes	Yes	No	Total	% Yes
Intermediate	7	57	64	10.9	9	38	47	19.1
Normal	53	261	314	16.9	56	286	342	16.4
Total	60	318	378	15.9	65	324	389	16.7
X-ray Evidence of COPD	Yes	No	Total		Yes	No	Total	
Present	21	50	71		25	78	103	
Absent	41	263	304		45	243	288	
Total	62	313	375		70	321	391	
% Present	33.9	16.0	18.9		35.7	24.3	26.3	
Total Responses[a]	64	327	391		73	332	405	

[a]Totals are not the same since some TIC and x-ray results were not available.

no significant difference between subjects having and not having this experience within the past month. Twelve subjects, 9 males and 3 females, indicated on questions 12 or 13 having "emphysema." An analysis of the symptoms experienced by the 12 subjects showed 8 had morning cough, 9 had three month cough, 10 had phlegm, 11 had wheeze, 6 had wheeze "most of the time", 9 had periodic wheeze "other than chest colds", 7 had x-ray evidence of COPD, and 8 had a grade 2 or more degree of breathlessness. The mean TIC value for male subjects was 0.73 mg/ml and for female subjects was 0.93 mg/ml. Six of the 10 subjects having "emphysema" previous to the last 3 years did not indicate having "emphysema" within the past 3 years.

The 2x2 frequency distributions of responses for male and female subjects with intermediate and normal levels of TIC were not significantly different. There was also no significant difference in the proportions of male and female subjects experiencing a recent chest illness.

The spirometry results of 63 male and 73 female subjects who had a recent chest illness had significantly lower spirometry means than the 324 male and 329 female subjects not having a recent chest illness.

The 2x2 frequency distribution of responses to having a recent chest illness with chest x-ray evidence of COPD indicated a significantly higher proportion ($p < 0.005$) of male subjects with as compared to without recent chest illnesses and chest x-ray evidence of COPD (33.9% vs 16 16.0%). There was also a significant difference ($p < 0.10$) for female subjects with a higher proportion having than not having a recent chest illness (35.7% vs 24.3%).

The mean TIC for male subjects with recent chest illnesses was

significantly higher ($p < 0.05$) than the mean TIC for male subjects not having recent chest illnesses. The TIC means were 0.741, 0.795, and 0.82 mg/ml for male subjects not having a recent chest illness, having a recent chest illness, and having a recent chest illness within the past month respectively. For female subjects, these values were 0.785, 0.790, and 0.872 mg/ml. No significant difference was noted between female subjects having or not having a recent chest illness.

Ease of Breathing

Question 9 on Form I was designed to measure a subject's difficulty in breathing; responses are ranked from normal indicated by grade 0 to severe difficulty indicated by grade 4. Table 16 shows the distribution of these frequencies with TIC levels and chest x-ray results.

A significant difference ($p < 0.05$) was indicated between the TIC levels for male subjects; however, no apparent pattern of responses could be detected in differentiating the distributions. Similar tests on female subjects were nonsignificant.

A comparison of the responses between male and female subjects showed no significant differences in their distributions.

The results of one way analysis of variance (AOV) tests with unequal sample sizes for male and female subjects showed the means of the spirometry variables to be significantly different ($p < 0.05$) among the 5 ease of breathing grades. As in the previous sections dealing with the presence or absence of COPD symptoms and spirometry results, no distinction has been made in determining which of the spirometric variables was the best. In general for each of the spirometric variables, grade 0 had the highest and grade 4 had the lowest mean values. Table 17 shows the

TABLE 16

DISTRIBUTION OF RESPONSES TO EASE OF BREATHING WITH INTERMEDIATE AND NORMAL LEVELS OF TIC AND WITH THE PRESENCE OR ABSENCE OF X-RAY EVIDENCE OF COPD BY SEX

Male

		Ease of Breathing Grades (0)	(1)	(2)	(3)	(4)
TIC Levels	Intermediate	26	23	9	2	4
	Normal	71	164	35	23	21
	Total	97	187	44	25	25
X-ray Evidence of COPD	Present	15	30	9	7	10
	Absent	82	156	35	16	15
	Total	97	186	44	23	25
	% Present	18.3	16.1	20.4	30.4	40.0
Total Responses[a]		101	194	45	25	26

Female

		Ease of Breathing Grades (0)	(1)	(2)	(3)	(4)
TIC Levels	Intermediate	9	25	10	1	2
	Normal	85	169	50	24	14
	Total	94	194	60	25	16
X-ray Evidence of COPD	Present	23	50	18	8	4
	Absent	72	140	43	20	13
	Total	95	190	61	28	17
	% Present	24.2	26.3	29.5	28.6	23.5
Total Responses[a]		99	199	62	28	17

[a]Totals are not the some since some TIC and x-ray results were not available.

means of one of the spirometric variables, $FEV_{1.0}$, for the 5 ease of breathing grades by sex.

TABLE 17

FEV(1.0) MEANS IN LITERS PER SECOND FOR SUBJECTS CLASSIFIED BY EASE OF BREATHING GRADES AND SEX

Subjects	Ease of Breathing Grades (0)	(1)	(2)	(3)	(4)
Male	3.17	3.06	2.91	2.35	2.13
Female	2.24	2.23	2.05	1.79	1.88

Additionally, to adjust for the effect of age on spirometric results, the spirometric variables $FEV_{1.0}$ and % $FEV_{1.0}$ were analyzed by a two way AOV with an unweighted-means solution to the problem of unequal cell sizes. A discussion of this procedure is given by Winer (50). This design is not an exact solution for the treatment of unequal cell sizes, but the test was used in this section as an approximation and the results should be interpreted accordingly. Male and female subjects were analyzed separately with age groups as one factor and ease of breathing grades as the second factor. Also for these two way AOV tests, the ease of breathing grades 3 and 4 were combined to eliminate zero frequencies.

The results of the AOV test for the spirometric variable $FEV_{1.0}$ showed no significant interaction effect between age groups and ease of breathing grades, but a significant difference ($p < 0.01$) among the $FEV_{1.0}$ means for age groups, and a significant difference ($p < 0.01$) among the $FEV_{1.0}$ means for the ease of breathing grades for both male and female

subjects. For the spirometric variable % $FEV_{1.0}$, the AOV test showed no significant interaction effect, no significant age group effect, but a significant difference ($p < 0.01$) among the % $FEV_{1.0}$ means for the ease of breathing grades for both male and female subjects.

In summary, the $FEV_{1.0}$ means decreased with an increase in age and with an increase in the degree of breathlessness and the % $FEV_{1.0}$ means decreased with an increase in the degree of breathlessness. Table 18 shows this general pattern of means for one of the age groups.

TABLE 18

FEV(1.0) AND % FEV(1.0) MEANS FOR SUBJECTS CLASSIFIED BY EASE OF BREATHING GRADES AND SEX FOR THE 40 - 49 YEAR AGE GROUP

$FEV_{1.0}$ (Liters per Second)				
Subjects	Ease of Breathing Grades (0)	(1)	(2)	(3,4)
Males	3.55	3.47	3.32	2.07
Females	2.33	2.42	2.28	2.15
% $FEV_{1.0}$				
Subjects	Ease of Breathing Grades (0)	(1)	(2)	(3,4)
Males	97.6	94.2	89.6	91.0
Females	86.2	88.2	86.3	82.0

The comparison of the distributions of responses to ease of breathing with the presence or absence of chest x-ray evidence of COPD was significant ($p < 0.05$) for male subjects but not for female subjects. Table 16 (p. 58) shows male subjects with increased difficulty in breathing also exhibiting a higher proportion of chest x-ray evidence of COPD than male subjects having no difficulty in breathing. Male subjects with severe ease of breathing grades 2, 3, and 4 had greater chest x-ray evidence than expected.

The results of one way AOV tests with unequal sample sizes for male and female subjects showed a significant difference ($p < 0.01$) among the TIC means for the 5 ease of breathing grades for male subjects but not for female subjects. Table 19 shows the TIC means for the ease of breathing grades for male and female subjects.

TABLE 19

TIC MEANS FOR SUBJECTS CLASSIFIED BY EASE OF BREATHING GRADES AND SEX

Subjects	Ease of Breathing Grades (0)	(1)	(2)	(3)	(4)
Males	0.71	0.76	0.75	0.80	0.82
Females	0.77	0.79	0.78	0.81	0.80

To control for the age effect on TIC values, a two way AOV was calculated as described above. The results showed the TIC means to be significantly different at the 5% level of significance for male subjects

but again were not significant for female subjects. The interaction effect of age and grades of breathlessness was also nonsignificant.

Both the one way and the two way AOV test results need to be examined carefully in this section since the one way confounds age, and the two way is a crude approximation.

Smoking History

Questions 1, 2, and 3 on Form I pertain to the subject's smoking history. The versatility of retrieval using the computer system previously mentioned in Chapter III enables one to investigate combinations of several variables in order to accurately describe the data and in this particular section to define a smoker. Arbitrary standards were used in distinguishing smokers from nonsmokers such as duration of smoking, pack years, and inhaling. The term pack year is the equivalent of one pack per day for the duration of one year or any equivalent product of packs per day times duration in years.

A total of 136 male subjects had smoked a pipe or cigar for at least one year and of this number 56 were smoking cigarettes now, 56 had smoked cigarettes but were not smoking cigarettes now, and 24 had never smoked at least 10 packs of cigarettes in their life. Also of the 102 who smoked pipes for at least one year only 11 had smoked for more than 10 years. Similarly for the 67 cigar smokers only 3 had smoked for more than 10 years. These results and the uncertainty of whether male subjects were smoking pipes or cigars now led to the exclusion of these factors in the arbitrary definition of smokers.

One measure of the effect of smoking may be tested by comparing spirometry means among selected groups of subjects. Based on the assump-

tion that true smokers would in general have lower spirometry means than nonsmokers, a search was made to find what standards would provide a reasonable number of smoking subjects satisfying this criterion.

Both male and female subjects who had smoked at least 10 packs of cigarettes in their life, 291 and 130 respectively, were younger in age and generally had similar or lower spirometric means than their counterparts. Out of the 291 male subjects who had smoked at least 10 packs of cigarettes in their life, 265 had inhaled; however, there was no significant difference between male subjects who inhaled compared to those who did not inhale. The TIC mean was higher, but not significantly, for male subjects who inhaled.

A group of male subjects was selected who had not smoked over 10 packs of cigarettes in their life and whose mean age was comparable to arbitrarily defined groups of smokers in order to compare spirometry results. This group of 52 male nonsmokers had significantly higher ($p < 0.01$) spirometry means than 170 male subjects who were smoking cigarettes now. Another retrieval selected 130 male subjects who were smoking cigarettes now and inhaling and had over 40 pack years of smoking history, or were smoking cigarettes now and inhaling and had 10-40 pack years of smoking history and had smoked cigarettes more than 10 years. The comparison of spirometry means between this group of smokers and the nonsmokers defined above also showed similar significant differences. The single criterion of smoking cigarettes now however showed greater significant differences than the combination of smoking now, inhaling, pack years, and duration of smoking cigarettes. Also in both groups of smokers the TIC means were significantly higher ($p < 0.005$) in comparison to the

select group of nonsmoking male subjects.

In the group of 130 female subjects who had smoked at least 10 packs of cigarettes in their life, 110 had inhaled and 97 were smoking cigarettes now. Comparisons between female subjects who inhaled versus those who did not and between female subjects smoking cigarettes now versus those not smoking now showed the means of the spirometric variables $FEV_{1.0}$ and FEF to be significantly lower ($p < 0.05$) for female subjects who inhaled or were smoking cigarettes now. The remaining spirometry results showed no significant differences.

The same logic as given above was used to define a group of 180 female nonsmokers and a group of 66 female smokers with various combined factors of smoking history. Similar results were obtained compared to the male groups of smokers and nonsmokers; that is, female smokers had lower spirometry means than female nonsmokers.

Using the single criterion of smoking cigarettes now or the combined criteria of various factor of smoking history, retrievals were formulated to explore the degree of COPD symptoms indicated by these groups. Besides having lower spirometry means, since this was a prerequisite in the selection of smokers initially, the retrievals showed male and female smokers also experienced a high proportion of COPD symptoms. Several of the higher proportions are discussed below.

In the group of 170 male subjects smoking cigarettes now, 59 (34.7%) had a morning cough, 39 (22.9%) had a cough for three months, 63 (37.1%) produced phlegm, and 82 (48.2%) had a wheeze. Slightly higher proportions occurred among male smokers defined by the combined criteria of smoking history. Another procedure in describing these findings is to

compare the occurrence of COPD symptoms among smoking groups with the total study population. Among male subjects indicating a morning cough, or a three month cough, or a wheeze, 59%, 60%, and 55.4% were smoking cigarettes now, respectively. In the two groups of female smokers, similar occurrences of high proportions of COPD symptoms were found. In many instances the proportion of smokers having COPD symptoms was twice as great as among the compliments of these groups. This observation was also true for male smokers.

These findings were utilized in the discriminant function method of analysis in the exclusion of select groups of subjects experiencing COPD symptoms that may in fact be primarily due to smoking.

Linear Discriminant Function Analysis

Linear discriminant functions were calculated on data from subjects classified into one of two mutually exclusive groups. All subjects with TIC determinations and complete data were separated into two groups based on having either intermediate or normal TIC levels. Male and female subjects were analyzed separately in each trial.

Several linear discriminant functions were investigated to determine which criteria and variables would adequately discriminant the two groups and would at the same time satisfy the hypothesis of subjects with intermediate TIC values exhibiting greater evidence of COPD symptoms than subjects with normal TIC values. Significance was determined by means of the F statistic for testing the difference between two p-dimensional mean vectors. An integral part of this F statistic is the generalized distance between two independent groups known as Mahalanobis' D^2. When significance between the mean vectors was found, further analyses were

performed to improve the difference.

Also with significant differences between intermediate and normal groups, the subjects were classified into either a high or low risk group based on the results of the linear discriminant function. High risk in this study is defined as the probability of having or developing COPD based on symptoms.

A score $x_j = \sum_{i=1}^{p} a_i X_{ij}$, where a_i, $i = 1,\ldots,p$ are the coefficients determined by the linear discriminant function and X_{ij} are the p observed variables for the j^{th} subject, was calculated for each subject and ranked numerically from lowest to highest to give the distribution function for each group. The distribution functions, I(x) for intermediate subjects and N(x) for normal subjects, can then be examined to determine sensitivity, specificity, false negative, and false positive rates for selected values of x. Sensitivity in this study is the probability of classifying subjects with intermediate TIC values into the high risk group while specificity is the probability of classifying subjects with normal TIC values into the low risk group. False positive and false negative rates are referred to as errors of misclassification. Ideally both sensitivity and specificity should approach 100% while misclassification errors are kept to a minimum; however, this outcome is not often met in the real world and hence some sacrifice in the accuracy of classification must be made. If the costs of misclassifying are assumed to be equal, then $\bar{x} = 1/2 \sum_{i=1}^{p} a_i(\bar{x}_{i1} + \bar{x}_{i2})$, where $\bar{x}_{i1}$ and $\bar{x}_{i2}$ are the means of the p-dimensional vectors of responses for the intermediate and normal groups, is the point at which misclassification is minimized. Other selected values of x can, for example, increase sensitivity at the expense of

specificity thus also decreasing the false negative rate while increasing the false positive rate.

Since emphysema is a very serious disorder, one would be willing to increase the false positive rate; that is, it would seem logical to classify more subjects with normal TIC values as belonging to the high risk group in order to accurately classify a high proportion of subjects with intermediate TIC values as belonging to the high risk group. This decision would certainly be beneficial when TIC determinations and supporting respiratory data were employed as a screening technique for more extensive studies. The costs of such studies could also be considered as a factor in the determination of high and low risk groups.

Table 20 shows the criteria and variable used in performing each analysis while Table 21 shows the results. Each successive analysis was run to find and improve the discrimination between subjects with intermediate and normal TIC levels.

Analysis number 1, with 13 variables and no restrictions, showed a significant difference between the mean vectors at the 10% level for male subjects, but the analysis did not show the subjects with intermediate TIC values possessing greater evidence of COPD symptoms than subjects with normal TIC values. On classifying the male subjects into either high or low risk groups and with $x = -0.80$, the sensitivity was 59.7%, specificity was 60.9%, and the misclassification errors were approximately 40%. By modifying x to equal -1.10 the sensitivity was increased to 79.0%, but the false positive rate increased to 57.1%.

Even though the F test result was not significant for the female subjects, the classification of female subjects into either high or

TABLE 20

CRITERIA AND VARIABLES CONSIDERED IN THE LINEAR DISCRIMINANT FUNCTION ANALYSES

Analysis Number	Subjects excluded in the Analysis	Variables												
		Morning Cough	Three Month Cough	Phlegm	Wheeze	Periodic Wheeze	Ease of Breathing	Age	FEV(1.0)	% FEV(1.0)	FEV(0.5)/FVC	FEV(1.0)/FVC	FEF	Chest X-ray
1	None	X	X	X	X	X	X	X	X	X	X	X	X	X
2	*, None	X	X	X	X	X	X	X	X	X	X	X	X	X
3	Less than 40 and greater than 70 years of age	X	X	X	X	X	X		X	X	X	X	X	X
4	Less than 30 and greater than 60 years of age	X	X	X	X	X	X		X	X	X	X	X	X
5	*,Less than 40 and over 70 years of age	X	X	X	X	X	X		X	X	X	X	X	X
6	With heart trouble	X	X	X	X	X	X		X	X	X	X	X	X
7	Smoking cigarettes now	X	X	X	X	X	X		X	X	X	X	X	X
8	Over 65 years of age and defined as smokers by combination of factors	X	X	X	X	X	X		X	X	X	X	X	X
9	Defined as smokers by combination of factors	X	X	X	X	X	X		X	X	X	X	X	X
10	Smoking cigarettes now	X	X	X	X	X	X	X	X	X	X	X	X	X
11	Over 70 years of age and smoking cigarettes now	X	X	X	X	X	X	X	X	X	X	X	X	X
12	Smoking cigarettes now	X		X		X		X		X		X	X	X
13	Smoking cigarettes now	X		X		X				X		X	X	
14	Smoking cigarettes now	X		X		X		X		X			X	
15	Smoking cigarettes now	X	X	X	X	X	X		X	X	X	X	X	
16	Smoking cigarettes now	X	X	X	X	X	X	X	X	X	X	X	X	
17	Smoking cigarettes now	X		X		X		X		X		X	X	

* TIC separation point for intermediate and normal levels was 0.52 mg/ml. for male subjects and 0.72 mg/ml. for female subjects.

TABLE 21

RESULTS OF THE LINEAR DISCRIMINANT FUNCTION ANALYSES

Analysis Number	Number of Variables	Male			Female		
		Number of Subjects Classified by TIC Levels			Number of Subjects Classified by TIC Levels		
		Intermediate	Normal	F	Intermediate	Normal	F
1	13	62	297	1.6 *	40	332	0.7
2	13	25	334	1.8 **	118	251	1.1
3	12	45	199	1.3	27	234	1.2
4	12	37	153	1.2	21	193	1.0
5	12	20	224	1.4	91	170	0.8
6	12	52	233	1.6 *	27	273	0.7
7	12	44	159	2.7 ***	31	252	0.5
8	12	39	108	1.4	23	198	1.0
9	12	48	176	2.1 **	33	273	0.6
10	13	44	159	3.0 ***	31	252	0.5
11	13	44	119	2.2 **	31	213	0.8
12	8	44	159	4.3 ***	31	252	0.6
13	6	46	167	1.6	36	258	1.2
14	6	46	167	5.5 ***	36	258	1.2
15	11	46	167	2.7 ***	36	258	0.7
16	12	46	167	3.1 ***	36	258	0.7
17	7	46	167	4.7 ***	36	258	1.0

* Significant at the 0.10 level
** Significant at the 0.05 level
*** Significant at the 0.01 level

low risk groups resulted in a sensitivity rate of 60.0% and a specificity rate of 59.6% when x = 0.93. By using x = 0.77, sensitivity rose to 82.5% while the false positive rate increased to 57.2%.

Analyses numbered 2 through 5 investigated selected age groups and different TIC separation points in defining intermediate and normal groups in an effort to improve discrimination. Analysis number 2 improved the level of significance to 5% for male subjects, but only contained 25 male subjects with TIC values less than 0.52 mg/ml. Five of the 13 variables showed greater evidence of symptoms of COPD among the intermediate group than among the normal group of subjects compared to only 3 of the 13 variables in analysis number 1. Similarly, the level of significance was improved for female subjects in analysis number 3, which was restricted to subjects between 40 and 70 years of age, but again at the expense of identifying only 27 female subjects in the intermediate group. Seven of the 12 variables examined in analysis number 3 for female subjects showed intermediate subjects possessing greater evidence of COPD symptoms. The remaining results for analyses numbered 2 through 5 were nonsignificant.

Analysis number 6 was performed by excluding subjects who indicated some form of heart trouble since these subjects exhibited a substantial proportion of COPD symptoms. The results were not too different than the results of analysis number 1.

Analysis number 7 was performed by excluding subjects who indicated smoking cigarettes now since these subjects also demonstrated having several COPD symptoms. The results of this analysis were significant for male subjects ($p < 0.01$) with 6 of the 12 variables showing

a greater evidence of symptoms among intermediate subjects and with the means of 4 additional variables being approximately equal. This analysis for male subjects will be discussed in a later section of this chapter. The result of the linear discriminant function was nonsignificant for female subjects in analysis number 7; in fact, all the results of the remaining analyses for female subjects were nonsignificant.

Analyses number 8 and 9 were performed by excluding subjects satisfying the combination of smoking history previously defined. These results were not as significant as using the single criterion of smoking cigarettes now.

Analyses numbered 10-17 dealt with the exclusion of all subjects smoking cigarettes now, with a reduction in the number of variable studied, and with the exclusion of chest x-ray results. Chest x-ray results were not used in analyses number 13-17 in order to test the reproducibility of the linear discriminant functions on a second set of data. This second set of data consisted of 219 intermediate and 218 normal subjects obtained in the respiratory study conducted in Muskogee County, Oklahoma during the Fall of 1972. Information from the results of the chest x-ray was not available for this study.

Results of Analyses Number 7 and 15

Analysis number 7 was performed with 12 variables and with the exclusion of all subjects smoking cigarettes now while analysis number 15 was identical in criteria and variables except for the exclusion of chest x-ray results. Both analyses showed the mean vectors between intermediate and normal groups to be significantly different ($p < 0.01$), and classifications into either high or low risk groups were similar.

Analysis number 7 actually resulted in lower false positive and false negative rates for a given sensitivity rate than did analysis number 15; however, analysis number 15 is discussed since this function can be tested on the second set of data.

For male subjects and with $\bar{x}$ = -0.538, the sensitivity rate was 69.6%, specificity rate was 62.9%, false negative rate was 30.4%, and the false positive rate was 37.1%. In comparison to analysis number 1 and with a similarly defined value for x, the sensitivity rate increased 10%. By modifying x to equal -0.97, sensitivity increased to 84.8% while the false positive rate increased to 57.5%. This is a slightly better classification than analysis number 1.

The coefficients determined by the linear discriminant function in analysis number 15 were applied on the same 11 variables in the second set of data to test its reproducibility. Classification of male subjects from the second set of data into either high or low risk group did not, however, yield acceptable results. According to this function,the sensitivity rate was 57.8% and the specificity rate was only 46.0% when $x = \bar{x}$. By modifying x to equal -2.45, sensitivity increased to 78.9% but the false positive rate increased to 76.2%.

Results of Analyses Number 10 and 16

Analyses number 10 and 16 were identical in criteria and variables to analyses number 7 and 15 respectively except for the inclusion of age as a variable. Analysis number 10 therefore had 13 variables and analysis number 16 had 12 variables with the exclusion of chest x-ray results. Results of both functions were similar with analysis number 16 being slightly more significant. The F tests for both analyses number 10 and 16

were greater than for either analyses number 7 or 15.

For analysis number 16 and with $\bar{x}$ = -5.80, sensitivity was 67.4%, specificity was 66.5%, while the misclassification errors were 32.6% and 33.5% respectively for false negative and false positive rates. By modifying x to equal -6.42, sensitivity was increased to 84.8% while the false positive rate increased to 56.8%. This last classification was slightly better than analysis number 7, which did not include age as a variable.

Results of Analyses Number 12 and 17

Analysis number 12 used 8 variables to improve the discrimination by eliminating those variables which did not contribute to the discrimination in the previous trials. Analysis number 17 was again identical in criteria and variables to analysis number 12 with the exception of chest x-ray results. Analysis number 17 produced a greater F test value than analysis number 12 and is discussed in more detail.

The result of analysis number 17 was also more highly significant than either analyses 7 and 15 or 10 and 16 with 6 of the 7 variables contributing to the discrimination. Five of the 7 variables--morning cough, periodic wheeze, $\%FEV_{1.0}$, $FEV_{1.0}/FVC$, and FEF--showed either a greater proportion of symptoms identified by the respiratory questionnaire or lower mean spirometry values among the intermediate than among the normal group of subjects. Although subjects with intermediate TIC values had a lower proportion of phlegm production than the subjects with normal TIC values, the negative coefficient determined by the linear discriminant function added to the discrimination between the two groups.

For male subjects and with $\bar{x}$ = -6.29, the sensitivity was 63.0%,

and specificity was 65.9%; however, with x = -6.85, sensitivity increased to 84.8% while the false positive rate increased to 52.1%. This second classification of male subjects into either high or low risk groups was again better than any previous classification in the sense of misclassifying fewer subjects.

Results of Analysis Number 14

Only 6 variables were used in performing analysis number 14 with highly significant results and with all 6 variables contributing to the discrimination between subjects with intermediate and normal levels of TIC. Three symptomatic variables--morning cough, phlegm, and periodic wheeze-- and two spirometry variables--$\%FEV_{1.0}$ and FEF-- were used. The inclusion of age as a variable basically resulted in a greater F value and it adds in the discrimination of the two groups. The mean age for male subjects with intermediate TIC values was 52.5 while the mean age was 60.4 for male subjects with normal TIC values. It is also worth noting that lower spirometry means occurred among subjects in the intermediate group compared to subjects in the normal group since spirometry values generally decrease with an increase in age.

For male subjects and with $\bar{x}$ = -6.63, sensitivity was 63.0% and specificity was 66.5%. By modifying x to equal -7.1, the false negative rate decreased from 37.0% to 15.2% and the false positive rate increased from 33.5% to 47.9%. Thus one is able to accurately classify 84.8% of the subjects with intermediate TIC values as belonging to the high-risk group while obtaining a moderately low false positive rate. Table 22 shows the two classifications discussed for this linear discriminant function in terms of changes in sensitivity, specificity, false positive, and

false negative rates and of corresponding numerical changes. By identifying 34 additional subjects as high risk (119 - 85), the sensitivity rate increased by 21.8% (84.8% - 63.0%) while the false positive rate increased by only 14.4% (47.9% - 33.5%). In numerical terms, however, 2 to 2 1/2 subjects with normal TIC values are included in the high risk group for each subject with intermediate TIC values being included in the high risk group.

TABLE 22

CLASSIFICATION OF MALE SUBJECTS WITH INTERMEDIATE AND NORMAL LEVELS OF TIC INTO EITHER HIGH OR LOW RISK GROUPS BY THE RESULTS OF LINEAR DISCRIMINANT FUNCTION NUMBER 14

	With $\bar{x}$ = -6.63			With x = -7.10		
TIC Levels	High Risk	Low Risk	Total	High Risk	Low Risk	Total
Intermediate	29 (63.0%)	17 (37.0%)	47	39 (84.8%)	7 (15.2%)	46
Normal	56 (33.5%)	111 (66.5%)	167	80 (47.9%)	87 (52.1%)	167

Unfortunately the linear discriminant function obtained in analysis number 14 did not produce satisfactory results when applied to a second set of data. The distributions of scores for subjects with intermediate as compared to normal TIC values were nearly identical. With x = $\bar{x}$, sensitivity was 46.7% and specificity was 49.2%. With x = -7.67, sensitivity was increased to 80.0% but the false positive rate increased to 84.1%.

Analysis number 15 (p. 72) provided a better linear discriminant

function in reproducing results on the second set of data than analysis number 14 even though analysis number 14 showed significantly greater differences in the mean vectors for male subjects with intermediate and normal levels of TIC.

CHAPTER V

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of deaths and disabilities in the United States with emphysema being the major contributor of this disorder. The discovery of a deficient proteinase inhibitor in human serum, alpha-1 antitrypsin, has been linked with the presence of COPD, particulary emphysema, and is currently being studied by several researchers throughout the world

Several authors have demonstrated a relationship between low levels of alpha-1 antitrypsin and COPD, but whether an association is also evident between intermediate trypsin inhibitory capacity (TIC) values and COPD remains speculative.

Because of the pathological definition of emphysema and the clinical definition of chronic bronchitis, the data does not permit accurate classification of the subjects as either having or not having COPD; therefore, in this study evidence of a subject having COPD was based on responses to a respiratory symptoms questionnaire, spirometry, and chest x-ray results. The presence of symptoms such as morning cough and periodic wheeze plus poor spirometry performance and chest x-ray evidence of COPD can readily be used as indicators of the presence of COPD.

The present study dealt both with a descriptive analysis of the

data and with the development of a model which would identify subjects suspected of having or developing COPD.

Descriptive Analysis

The data was investigated for possible relationships between age, sex, and TIC values, for comparisons between the presence or absence of COPD symptoms identified on the questionnaire with spirometry and chest x-ray results, and for comparisons between intermediate and normal levels of TIC with the presence or absence of COPD symptoms.

These investigations showed male subjects had a significantly lower TIC mean than female subjects, TIC values for male subjects increased linearly with age, and TIC values for female subjects followed a quadratic distribution with a minimum at age 62.57. The fitting of a polynomial to a set of data points does not, however, imply whether the fit is good or not. The ratio of the sum of squares due to regression to the total sum of squares is a measure of the amount of variabilty explained by the regression line. For both the linear and quadratic lines, these ratios were low indicating a poor fit; nevertheless, an age by TIC trend was observed in this study.

Whether these TIC distributions for male and female subjects are due to other factors can not be determined from the present data. One would like to know whether TIC values for a particular individual increase as the subjects grows older or do subjects with low and intermediate TIC values die sooner than subjects with normal TIC values. Also, pregnancy and the use of oral contraceptives have been associated with increased TIC values and could thus account for the quadratic distribution found in female subjects as well as the higher TIC mean than for male subjects.

The analysis of each variable presented in Chapter IV yielded some interesting results and conjectures. The mean spirometry variables were significantly lower for subjects having a particular symptom such as morning cough or wheeze than for subjects not having this symptom. The presence of symptoms as identified by the questionnaire did affect the subjects' ventilatory capacity. All comparisons in this aspect of the study were also examined for age differences in the subjects since spirometry results are influenced by this factor; however, age was not a factor in most of the comparisons since the mean age differences were non-significant, but was noted in the analyses of periodic wheeze, chest x-ray, heart trouble, and ease of breathing. Other factors such as obesity and smoking history may also influence a subject's spirometry performance but were not examined in this study.

The comparisons of chest x-ray results with symptoms identified on the questionnaire indicated little association between chest x-ray evidence of COPD and the presence of symptoms. Significant differences were indicated for female subjects with morning cough and three month cough, and for male subjects with wheeze, periodic wheeze, recent chest illnesses, and ease of breathing. All the remaining comparisons were non-significant. Information obtained through a single chest x-ray in the survey of a community population may well be viewed with some degree of skepticism because of the difficulties encountered in interpreting the chest x-rays accurately and reliably.

Thus in this study the associations between COPD symptoms identified on the questionnaire and chest x-ray evidence of COPD were not as objective and conclusive as was the case with spirometry results.

One may surmise however that questionnaires pertaining to COPD symptoms can be instrumental in obtaining information relating to the disease itself, although the validity of the responses in any study depends on the qualifications and training of the interviewers. Also in the study of community populations, the questionnaire may be the only feasible method of obtaining information.

One of the primary objectives of this study was to test whether subjects with intermediate TIC values experienced greater evidence of COPD symptoms than subjects with normal TIC values. Higher proportions of symptoms such as morning cough, wheeze, and phlegm or lower spirometry means, or chest x-ray evidence were suspected of occurring more frequently among male subjects with intermediate TIC values.

In the analyses of each variable separately, no significant differences were found in the comparisons of subjects with intermediate TIC values to subjects with normal TIC values for the variables morning cough, wheeze, three month cough, phlegm, periodic wheeze, chest x-ray, and recent chest illness. Each of these analyses were performed on male and female subjects separately and used 0.62 mg/ml as the separation point between intermediate and normal levels. The 2x2 Chi-square test was the statistical test used in each comparison. For two of the variables, wheeze and periodic wheeze, significant differences occured for male subjects when 0.49 mg/ml was used as the separation point between intermediate and normal levels of TIC. Other attempts to find a separation point which would lead to further significant differences in the distributions of each variable were either nonsuccessful or in many instances were found to be at a point whereby more than one-half of the subjects would

be classified as intermediate. This is contrary to all published reports dealing with the prevalence of low, intermediate, and normal levels of TIC in a given population.

The results of these analyses lend little support to the hypothesis in question; however, other factors must be taken into account before a final conclusion can be determined. Differences in TIC distributions, spirometry results, and in the distributions of responses on the questionnaire between male and female subjects were observed early in the study and consequently male and female subjects were analyzed separately. Other factors such as age, smoking history, and a history of heart trouble also have a notable influence on the subjects's spirometry performance and in the responses given on the respiratory questionnaire. The occurrence of COPD symptoms among subjects with heart trouble or among subjects defined as smokers, who also had normal TIC values, would mask any true differences between subjects with intermediate and normal levels of TIC. Both subjects with heart trouble and subjects defined as smokers were found to possess a high proportion of COPD symptoms and were subsequently excluded from some trials of the linear discriminant function analyses.

The definitions of smokers arrived at in this study and the ensuing results were another area deserving further investigation. In an attempt to define a subject as a smoker, the single response to the question of smoking cigarettes now produced greater differences between the defined group of smokers and a group of smokers than a combination of smoking history including inhaling, duration, and pack years. Interestingly, no significant differences in spirometry results were obtained

in the comparisons between male subjects who inhaled and subjects who smoked but did not inhale. Male subjects smoking cigarettes now did, however have significantly lower spirometry means than male subjects who had smoked cigarettes but were not smoking now. Most of the female subjects who had smoked at least 10 packs of cigarettes in their life also inhaled and were smoking cigarettes now.

Increased TIC means were observed among subjects having symptoms such as wheeze, periodic wheeze, and recent chest illness compared to subjects not indicating these symptoms. This observation may be due to the occurrence of many of these symptoms among subjects with heart trouble or subjects defined as smokers who also had normal TIC values. It has been noted that recent infections may also increase the subjects' TIC determination. In this study, TIC means were much higher among subjects indicating a recent chest illness within the past month compared to subjects having a chest illness in the past three years or subjects not having a chest illness.

Finally, the differences in TIC distributions and occurrences of symptomatology together with the lower mortality experience among female subjects as compared to male subjects may suggest the existence of a protective mechanism among female subjects.

Linear Discriminant Function Analyses

A total of 17 linear discriminant functions were performed, using different selection criteria and variables, in order to derive a function which would discriminate between two groups of subjects. Subjects were classified into either intermediate or normal groups if their TIC values were classified as intermediate or normal respectively. Lin-

ear discriminant functions were performed separately for male and female subjects because of the differences in TIC distributions, spirometry, and responses to the respiratory questionnaire.

The computation of Mahalanobis' generalized distance between two groups and the assumption of the variables in each group following a multivariate normal distribution with the same though unknown covariance matrix are the basics needed in performing the linear discriminant function method of analysis. The normality assumption is utilized in deriving tests of significance between the two mean vectors by means of the F statistic. Whether the assumptions of normality and homogeneity of variance are met is questionable; however, the distribution of scores for the subjects in each group in these analyses had nearly identical variances.

Thus in this study, the methods of linear discriminant analysis were used both in developing a model which would identify intermediate subjects as belonging to a high risk group and in showing the mean vector of responses for subjects with intermediate TIC values to be more indicative of having or developing COPD than subjects with normal TIC values. This model can then be applied to other sets of data to predict its reproducibility under the assumptions that a true difference does exist between subjects with intermediate and normal levels of TIC. The model itself is a linear combination of the variables such that each subject in both groups is classified into one of two categories denoted by high and low risk groups. Sensitivity was defined as the probability of correctly classifying intermediate subjects into the high risk group, and specificity is therefore the probability of classifying subjects with normal TIC values into the low risk group.

Two major problems were encountered early in the study; first of all, some criteria had to be found which would lead to significant differences between the mean vectors, and secondly, these criteria needed to demonstrate greater evidence of COPD among subjects with intermediate as compared to normal TIC values. Of the 17 analyses performed, the analyses dealing with the exclusion of subjects smoking cigarettes now were most significant particularly for male subjects. The effect of excluding these subjects resulted in a higher proportion of intermediate subjects indicating COPD symptoms such as morning cough, wheeze, and periodic wheeze and lower spirometry means compared to subjects with normal TIC values. The intermediate group of subjects had lower spirometry means even though the average age was 8.2 year lower than the group with normal TIC values. Analyses number 7, 10, 12, 14, 16, and 17 dealt primarily with the exclusion of subjects smoking cigarettes now, but varied in the number of variables studied. These successive analyses not only discriminated between intermediate and normal groups of male subjects, but also demonstrated greater evidence of COPD symptoms for male subjects with intermediate TIC values.

Of the 5 times when male subjects were classified into either high or low risk groups by means of the linear discriminant function, analysis number 14 resulted in the best classification. In this trial, 84.8% of the male subjects with intermediate TIC values were classified as high risk while 47.9% of the male subjects with normal TIC values were classified into the high risk group. If the purpose of these data were to provide information in the selection of subjects for more detailed examinations and the linear discriminant function method of analysis was

utilized in the decision making process of which subjects would be further examined, then 39 (84.8%) of the 46 subjects with intermediate TIC values and 80 (47.9%) of the 167 subjects with normal TIC values would be asked to participate.

Other criteria besides smoking cigarettes now did not lead to successful results for male subjects in this study although some additional selection of subjects may have produced better discriminant functions. A lower value of separating intermediate and normal levels of TIC for male subjects may be one criterion worth further investigation.

Other criteria besides those used in this study may also result in better discriminant functions for female subjects. Perhaps a combination of selected age groups, altered separation points between intermediate and normal levels of TIC, or a different selection of variables could be investigated.

The same criteria and variables for analyses number 14 and 15 together with the coefficients of the variables for these functions were applied to a second set of data obtained during a similar respiratory study conducted in Muskogee County, Oklahoma. The discriminant functions did not produce similar results compared to the original set of data, but instead raise additional questions about this area of medical research. The two data sets had one major difference which may partially explain the obtained results. The second set of data from Muskogee County differed in the method of obtaining subjects with normal TIC values. For each subject with an intermediate TIC value in Muskogee County, a subject with a normal TIC value and matched by age, sex, and race was selected. Thus the differences in mean ages would not be a factor as was the case

in the original set of data from Seminole County, Oklahoma.

Also, as a result of the linear discriminant functions not reproducing similar results, the basic question of whether subjects with intermediate TIC values have any greater evidence of COPD symptoms than subjects with normal TIC values remains questionable. As mentioned earlier in the discussion, however, perhaps other factors or combinations of factors relevant to this area of medical research need to be examined.

CHAPTER VI

SUMMARY

Data from an epidemiological study of emphysema and chronic bronchitis was statistically described in relating symptoms of chronic obstructive pulmonary disease (COPD) to a newly discovered factor in a subject's sera and was utilized in developing a model which would identify subjects suspected of having or developing COPD.

Subjects classified as having intermediate trypsin inhibitory capacity (TIC) values were compared to subjects having normal TIC values to determine whether the former group had greater evidence of COPD symptoms than the latter group. When each variable was discussed separately, few significant differences were observed between these two groups; however, by means of linear discriminant functions and by excluding from the analyses subjects who indicated smoking cigarettes now, discrimination was obtained with greater evidence of COPD symptoms among male subjects with intermediate as opposed to normal levels of TIC. The results of these discriminant functions were used to classify intermediate and normal groups of subjects into either a high or low risk group. The best classification described in this study assigned 84.8% of the intermediate group of male subjects into the high risk group and 52.1% of the normal group of male subjects into the low risk group. No significant dis-

criminating functions were found for female subjects.

Two of the models were applied to a second set of data in order to test their reproducibility. The results were not reproducible and consequently raise some questions as to whether subjects with intermediate TIC values experience greater evidence of COPD symptoms than subjects with normal TIC values, or whether other criteria need to be examined in these analyses.

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APPENDIX

FORM I

Directions: Place the number corresponding to the interviewee's response in the space provided in the right margin. Fill in additional information as directed. Code in "do not know" responses as "0".

Name _____ (Last First Middle)

Address _____ (Street or RFD)

_____ (City State)

Telephone _____

Column (1) 1

Subject number (2-6)_____

Interviewer (7-8)_____

Date_____

Birth Date_____ (mo. day year)

Birth Place_____ (City State)

* *

Age: 1. 15-34
2. 35-54
3. 55 and up
(9)_____

Sex: 1. Male
2. Female
(10)_____

Race: 1. White
2. Negro
3. Indian;_____ (tribe)
4. Other;_____ (specify)
(11)_____

Marital Status: 1. Married
2. Single
3. Widowed
4. Divorced
5. Separated
(12)_____

Occupation_____ Code_____

Education_____ Code_____ _____ (index) (13)_____

Occup. Head of Household_____ Code_____

Education of Head of Household_____ Code_____ (14)

_____ (index)

Are you a veteran? 1. Yes 2. No (15)_____

If yes: When? 1. 1889-1903 (16)_____
2. 1917-1918
3. 1941-1946
4. 1950-present

1. Have you smoked as much as 10 packs of cigarettes in your life?

1. Yes 2. No (17)_____

If yes: At what age did you start? _____ (18)_____
fill in

1. under 5
2. 5-14
3. 15-24
4. 25-34
5. 35-44
6. 45-54
7. 55-64
8. 65-74
9. 75 and up

Do you inhale? 1. Yes 2. No (19)_____

Are you smoking now? 1. Yes 2. No (20)_____

If no: At what age did you stop? _____ (21)_____
fill in

1. under 5
2. 5-14
3. 15-24
4. 25-34
5. 35-44
6. 45-54
7. 55-64
8. 65-74
9. 75 and up

In all, how many years have you smoked? _____ (22)_____
fill in

1. under 1
2. 1-4
3. 5-10
4. 11-19
5. 20-39
6. 40 and up

2. How many packs of cigarettes per day did you smoke during you first 2 years of smoking?

_____ x2
fill in

How many per day since then?

_____ x

Have your smoking habits changed since your second year of smoking for a period of a year or more, for instance, did you stop smoking for a while?

1. Yes 2. No (23)_____

If yes: How many packs per day did you smoke during this time?

_____
fill in

For how many years?

_____
fill in

Pack years lost (K): _____
fill in

Where K=(packs per day x years duration).

a) Average packs per day _____

b) Pack years ("a" x years smoked plus or minus "K")_____

Code in "b" above only (24)_____
1. under 10
2. 10-40
3. 41-80
4. 80 and up

3. Have you ever smoked a pipe for more than one year?
1. Yes 2. No (25)_____

If yes: For how many years? (26)_____
1. 1-4
2. 5-10
3. 11-19
4. 20-39
5. 39 and up

Do (did) you inhale? 1. Yes 2. No (27)_____

Have you ever smoked at least one cigar per day for a year or more?
1. Yes 2. No (28)_____

If yes: For how many years? (29)_____
1. 1-4
2. 5-10
3. 11-19
4. 20-39
5. 39 and up

Do (did) you inhale? 1. Yes 2. No (30)_____

4. Have you ever worked for at least 1 year in a trade where you were exposed to:

a) dust 1. Yes 2. No (31)_____

If yes: Did you work in: (32-33)_____
1. asbestos
2. sandblasting
3. stoneworking
4. cotton gin
5. mining
6. grain or hay
7. other _____
fill in

For how long? (in years) (34)_____
1. 1-5
2. 6-10
3. 11-19
4. 20 and up

b) Gases or fumes?
1. Yes 2. No (35)_____

If yes: What kind of work? (36-37)_____
1. welder
2. smelter (or steel mill)
3. tar
4. insecticides
5. paints or solvents
6. other_____ fill in

For how many years? (38)_____
1. 1-5
2. 6-10
3. 11-19
4. 20 and up

c) If yes to "a" or "b" above: Did you use protective equipment?
1. Yes 2. No (39)_____

5. Do you usually cough when you first get up in the morning?
1. Yes 2. No (40)_____

If yes: How many years have you done this? (41)_____
1. under 1
2. 1-5
3. 6-10
4. 11 and up

Do you go on coughing during the day? (42)_____
1. Yes 2. No

If yes: How many years have you done this? (43)_____
1. under 1
2. 1-5
3. 6-10
4. 11 and up

6. Do you have a cough for three months or more during the year? (except when you have a cold)
1. Yes 2. No (44)_____

If yes: How many years have you had this: (45)_____
1. under 1
2. 1-5
3. 6-10
4. 11 and up

7. Do you usually cough up phlegm from your chest? (not nose)
   1. Yes 2. No (46)_____

   If yes: How many years have you done this? (47)_____
   1. under 1
   2. 1-5
   3. 6-10
   4. 11 and up

   In the morning? 1. Yes 2. No (48)_____

   Late in the day? 1. Yes 2. No (49)_____

   What is the color of the material coughed up? (50)_____
   1. clear,white,grey
   2. occas. yellow/green
   3. usually yellow/green

8. Have you ever coughed up blood? 1. Yes 2. No (51)_____

   If yes: For how many years? (52)_____
   1. under 1
   2. 1-5
   3. 6-10
   4. 11 and up

   How much blood? (53)_____
   1. streaks
   2. more

9. Ease of breathing: (code of highest grade only) (54)_____

   1. Grade #1: Are you short of breath when walking fast on level ground or when walking up a hill?
   2. Grade #2: Are you ever short of breath on light exericise, i.e., walking at a normal pace?
   3. Grade #3: Do you have to walk more slowly than most people on level ground because of being short of breath?
   4. Grade #4: Are you too breathless to leave the house, or out of breath after dressing or undressing?

10. Does your breathing ever sound wheezy or whistling?
    1. Yes 2. No (55)_____

    If yes: Is this: (56)_____
    1. only occasionally (i.e. with colds)
    2. most of the time

11. Have you ever had periodic attacks of wheezing and breathlessness?
    1. Yes 2. No (57)_____

    If yes: Other than with chest colds:
    1. Yes 2. No (58)_____

If yes: Age when this started? (59)_____

1. under 14
2. 15-34
3. 35-54
4. 55 and up

Age this stopped: (60)_____

1. under 14
2. 15-34
3. 35-54
4. 55 and up

Do you have these attacks now?

1. Yes 2. No (61)_____

Is there anything which brings on (causes) your attacks of wheezing and breathlessness?

1. Yes 2. No (62)_____

What specifically?_____
fill in

Do you wheeze more in: (63)_____

1. Summer
2. Fall
3. Winter
4. Spring
5. No difference

12. During the last three years have you had a chest illness which kept you off work or at home indoors?

1. Yes 2. No (64)_____

If yes: What illness: (65)_____

1. Pneumonia
2. Pleurisy
3. Tuberculosis
4. Bronchitis
5. Emphysema
6. Other_____
fill in

Was this illness within the past month?

1. Yes 2. No (66)_____

Was is accompanied by: Increased cough?

1. Yes 2. No (67)_____

Increased phlegm?

1. Yes 2. No (68)_____

How many days did this illness last? (69)_____

1. under 1
2. 1-4
3. 5-8
4. 8-20
5. 21-60
6. 60 and up

How many of these illnesses have you ever had in your life? (70)_____

1. 1
2. 2-5
3. 6-10
4. 11 and up

13. Except for the **last** three years have you ever had any of the following chest illnesses? (71-72)_____

1. Pneumonia
2. Pleurisy
3. Tuberculosis
4. Bronchitis
5. Emphysema
6. Other_____(fill in)
7. None of these

If yes: At what age(s)? (73-74)_____

1. under 14
2. 15-34
3. 35-54
4. 55 and up

14. Have you ever had heart trouble?

1. Yes 2. No (75)_____

If yes:

1. Heart failure? (76-77)_____
2. Heart attack or angina?
3. High blood pressure?
4. Rheumatic fever?
5. Other_____ fill in

15. Is there any chest disease in your family?

1. Yes 2. No (78)_____

If yes:

1. T. B.? (79)_____
2. Emphysema?
3. Chronic Bronchitis (chronic cough)?
4. Other?

Disease	Relationship
_____	_____
_____	_____
_____	_____
_____	_____

FORM II

Seminole County COPD Study

Column (1) 2

Subject No. (2-6)_____

(7)_____

Study Date:

1. December
2. May
3. Unknown

Height (in inches) (8-9)_____

Weight (in pounds) (10-12)_____

Age (in years) (13-14)_____

(15)_____

Sex:

1. Male
2. Female
3. Unknown

Spirogram:

F.V.C. (liters) Observed (16-17)_____

F.V.C. (liters) Predicted (18-19)_____

*Percent of Predicted (20-22)_____

FEV-0.5 (liters) Observed (23-24)_____

FEV-0.5 (liters) Predicted (25-26)_____

*Percent of Predicted (27-29)_____

FEV-1.0 (liters) Observed (30-31)_____

FEV-1.0 (liters) Predicted (32-33)_____

*Percent of Predicted (34-36)_____

*FEV-0.5/FVC Observed (37-38)_____

*FEV-1.0/FVC Observed (39-40)_____

FEF (L./sec.) Observed (41-42)_____

FEF (L./sec.) Predicted (43-44)_____

*Percent of Predicted (45-47)_____

FEF within 2 S.D. of expected? (48)_____

1. Yes
2. No

Antitrypsin Immunodiffusion (1:x) (49-51)_____

Trypsin Inhibitory Capacity (mg/ml) (52-54)_____

Mycoplasma pneumonia antibody:
Code "1" if positive at 1:20

Procedure: MI (55)_____

CF (56)_____

CA (57)_____

TRI (58)_____

X-ray: Evidence of COPD? (59)_____

1. Present
2. Absent