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ARM1.950119.011a

DATE SUBMITTED 09 Jun 93
DATE IRB APPROVED 20 Jul 93
DATE CDR APPROVED 22 Jul 93
PROTOCOL NO. ASSIGNED 93/44

WILLIAM BEAUMONT ARMY MEDICAL CENTER
El Paso, Texas 79920-5001

Application for Clinical Investigation Project

1. PROJECT TITLE: Early Cardiopulmonary Exercise Abnormalities in Asymptomatic Smokers.

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3. LOCATION OF STUDY: Human Performance Laboratory, Department of Clinical Investigation, William Beaumont Army Medical Center, El Paso, TX 79920-5001.

4. TIME REQUIRED TO COMPLETE: 2 years (01/94 to 01/96).

5. INTRODUCTION:

a. Synopsis: Early detection of cardiopulmonary abnormalities in asymptomatic smokers would play a major role in helping to target individuals who may be at higher risk for the development of heart and/or lung disease. Such early detection would allow more timely and aggressive smoking cessation as well as other cost effective therapeutic intervention programs. The scope of the smoking problem remains enormous despite recent trends in the U.S.A. towards greater smoking cessation. Smoking remains the leading cause of chronic obstructive pulmonary disease (COPD) in the U.S. and a major risk factor for coronary heart disease. Unfortunately, approximately 25% of Americans are current smokers (Lung disease data, 1993); smoking cessation programs have a success rate of only 15-35% after 1 year (Paoletti 1993). Furthermore, smoking habits for military personnel, future VA beneficiaries, are even worse (Ballweg 1989).

A variety of resting cardiopulmonary tests have been unable to reliably predict which asymptomatic smokers would be at higher risk for the development of heart and/or lung disease. Alternatively, several investigators using exercise in military and civilian subjects have shown consistent differences in exercise performance (Sue 1985; Cooper 1968; McHenry 1977; Daniels 1986) and pulmonary gas exchange (Frans 1975, Sue

1985) between smokers and non-smokers. The results of these studies, however, are clouded by poor characterizations of the groups with respect to level of fitness, concurrent conditions, abnormalities of resting PFTs, description of symptoms, etc.

We propose a study with the following hypothesis: that asymptomatic smokers with normal resting cardiopulmonary function (PFTs, ECG) may have early stages of peripheral airway disease and/or occult heart disease that would be manifested during the stress imposed by maximal cardiopulmonary exercise testing. We anticipate that cardiopulmonary exercise testing would demonstrate differences in aerobic capacity as well as other more subtle differences in flow-volume relationships and/or pulmonary gas exchange and possibly abnormal cardiovascular response patterns between smokers and non-smokers.

Objectives: 1) To determine whether aerobic capacity ($\dot{V}O_2$ max) and other more subtle differences in the cardiopulmonary response to exercise can be detected between asymptomatic smokers and a well matched control group of non-smokers. 2) If differences are observed, to analyze the relationship between the abnormal measurements with the smoking history, resting PFT's, and coronary risk stratification analysis. 3) To detect a sub-population of smokers with abnormal cardiopulmonary response to exercise and generate a data base for future studies that would determine if these smokers represent subjects who are at higher risk for the development of full blown COPD and/or coronary heart disease.

Procedure: Sixty asymptomatic smokers with normal ECG and spirometry and 60 well matched controls will be studied. Volunteers will be recruited from the Sergeants Major Academy, Fort Bliss. A maximal incremental cycle ergometry exercise test with radial arterial line will be performed. Aerobic capacity and many other cardiopulmonary variables will be measured. After a 2 hour rest, a constant work multistage exercise test will be performed for mechanics of breathing determinations and pulmonary gas exchange measurements.

The likelihood of detecting differences between these well matched smokers and non-smokers is high. As noted, previous studies have consistently shown differences in the exercise response between these 2 groups, although the characterization of the subjects was poor and many other factors masked the results. This study provides a unique opportunity for dual functional assessment and early detection of cardiopulmonary abnormalities in individuals who may be at higher risk for the development of heart and/or lung disease.

The risk of exhaustive exercise under controlled testing conditions in previously screened, physically active subjects (active duty military) is minimal. The placement of an arterial catheter represents the only greater than minimal risk that will be encountered compared to routine field conditions. Very rare complications include hematoma, thrombosis, local infections and ischemia of the hand; some subjects experience minor

wrist discomfort that usually lasts less than 24 hours and resolves without sequelae.

The Human Performance Laboratory has studied exercise performance in over 200 research volunteers over the last 8 years without incident related to procedures.

b. Military Relevancy: The proposed work has enormous relevance to both the military and VA patient care mission. The magnitude of the smoking problem as has been noted is impressive (Redline 1991, Brockie et al 1990). A comparison of health habits of military vs. civilian populations revealed that smoking habits of military personnel, future VA beneficiaries, were less favorable than those of civilians (Cronan et al 1988, Ballweg et al 1989). There were more current smokers (43% vs. 32.6%) and fewer former smokers (19.3% vs. 30.9%) for military vs. civilian population, respectively. This means that problems due to smoking, notably of the heart and lungs, will be more prevalent as the military population ages, leaves service and joins the civilian sector. The VA will be one of the health care conduits through which eligible individuals will seek medical care. It would be more cost effective in the long run for the military and VA to engage innovative and comprehensive approaches to early detection and effective therapeutic strategies in smokers who are at risk for the development of COPD and/or coronary heart disease (CHD) rather than solely concentrating on treatment of chronic irreversible diseases.

c. Objectives:

1. To recruit a group of asymptomatic smokers with at least a 15 pack years smoking history and normal spirometry and carefully match them by age, race, and activity level to a comparable group of non-smokers. Both groups will be well characterized based on extensive health questionnaire responses, complete baseline PFTs (spirometry, lung volumes, diffusing capacity of carbon monoxide [DLCO], selected "small airway" tests), bronchial hyperreactivity testing and coronary risk stratification analysis. The results of previous studies (Cooper et al 1968, Daniels et al 1984, Sue et al 1985) that have attempted to evaluate cardiopulmonary differences between smokers and non-smokers were clouded by poor characterization of the populations studied with respect to: level of physical activity, carboxyhemoglobin (COHb) level, concurrent conditions, abnormalities of resting PFTs, and description of symptoms, etc.

2. To determine whether maximal exercise testing is an effective diagnostic tool for the early detection of cardiopulmonary abnormalities in asymptomatic smokers.

a. To determine if exercise capacity as determined by a $\dot{V}O_2$ max and by 2 mile run time is different between asymptomatic smokers and non-smokers (Daniels et al 1986, Bahrke et al 1986) when physical activity level and COHb are controlled.

b. To determine whether other more subtle differences in the cardiopulmonary response to exercise can be detected between asymptomatic smokers and non-smokers. These may include pulmonary gas exchange abnormalities (Frans et al 1975) and abnormal tidal flow-volume loop differences as indicators of early expiratory flow limitation

which in asymptomatic smokers may only be seen at maximal exercise. Both of these types of abnormalities would possibly be reflective of "peripheral airways" dysfunction. Also, subtle cardiovascular patterns suggestive of occult heart disease may also be discerned.

3. To relate the cardiopulmonary abnormalities observed in asymptomatic smokers to various components of the health questionnaire including smoking history, activity level, coronary risk analysis, etc. and to resting PFTs and results of a bronchial hyperreactivity testing.

4. To generate a data base of asymptomatic smokers with and without abnormal cardiopulmonary response to exercise.

d. Study design: Prospective controlled study.

e. Type of subject population observed: Volunteers will be recruited from the Fort Bliss Sergeants Major Academy. The Sergeants Major Academy trains approximately 500 senior enlisted Army personnel every six months with an age range of 30-50 yrs, mean age = 40 years; 38% of them are smokers.

f. Status/Background:

Smoking Habits in the Civilian and Military Sectors: Smoking continues to be a serious public health problem. Despite all the effort and money invested in anti-smoking campaigns, more than one fourth of the U.S. population are smokers (Lung disease data 1993) and 30 to 50% of the adult population in Europe is still smoking (Tobacco smoking 1986). Besides lung cancer, smoking remains the leading cause of COPD and a major risk factor for CHD. (Janoff et al 1987, Wilhelmsen 1988). There are more than 15 million Americans affected with COPD and this entity is the fifth leading cause of death in the U.S. (Redline 1991). Cardiovascular diseases are the most important cause of mortality in our society (Brockie et al 1990).

The logical solution to diseases caused by smoking is to encourage greater smoking prevention and cessation. Although there has been considerable progress in smoking prevention especially among young men (DHHS 1989, Pierce et al 1989), the success rate for smoking cessation among established smokers and young women is poor (Belt 1990). Of those who make a serious attempt to quit, only 15% to 35% remain smoke free after 1 year (Abelin et al 1989, Transdermal 1991). It would appear that despite intense public health campaigns for smoking cessation, some individuals cannot or will not stop smoking (Paterson et al 1988).

The smoking habits of military personnel are even worse than those of civilians; the percentage of current smokers in the Navy (50%) is almost double that of the civilian population (25%), with many starting to smoke after enlistment (Cronan et al 1988). Recently, a comparison of health habits of military vs. civilian populations revealed that

smoking habits of military personnel, future VA beneficiaries, were less favorable than those of civilians. There were more current smokers (43% vs. 32.6%) and fewer former smokers (19.3% vs. 30.9%) for military vs. civilian populations, respectively. The authors suggested that anti-smoking campaigns were more effective with the civilian population than with the military (Ballweg et al 1989).

Smoking, "Small Airway" Abnormalities - COPD

Multiple studies have convincingly demonstrated that cigarette smoking is the strongest determinant of COPD (Griffith et al 1989). It has been demonstrated that exposure to cigarette smoke will result in alteration of the structure of the small airways through several mechanisms (Janoff et al 1987). The host factor plays a critical role, since it is unclear why a large proportion of smokers do not develop COPD (Idell et al 1989; Wright et al 1992a; Janoff et al 1987). The pathology reported in the small airways of smokers is considered to represent an early stage in a continuous progression towards COPD (Wright et al 1992). From a physiologic perspective, the contribution of the small airways to the total lung resistance is less than 25% in the normal lung (Hogg et al 1968); this makes it very difficult to evaluate mild functional abnormalities in this segment of the airways. When the obstruction is located in the central and/or large airways, conventional spirometry is more than adequate to detect airflow limitation in these segments. Since, in the proposed work, we are looking for early detection of cardiopulmonary abnormalities in asymptomatic smokers, only subjects with normal spirometry (normal force vital capacity [FVC], normal force expiratory volume in one second [FEV_1], normal FEV_1%) using standard ATS (1991) criteria will be studied.

The significance of the purported tests of small airways disease such as: dynamic compliance, closing volume, volume of isoflow and flows at low lung volumes is very controversial. Although several studies have shown significant differences in the results of these tests between smokers and non-smokers (Berend 1983; Bates 1992), the power of the small airways tests to predict which smokers would develop chronic airflow obstruction has not been consistently demonstrated (Griffith et al 1989). Also, an inconsistent correlation between abnormal small airways tests and pathological changes has been reported. Improvement in small airway diseases has been demonstrated with smoking cessation without improvement in the inflammatory changes of the airways (Wright et al 1988). Furthermore, the physiologic parameters being correlated with the pathologic changes may not become abnormal until the pathologic abnormality is of significant magnitude (Wright 1992b). Lastly, there have been no studies to our knowledge that have attempted to correlate "small airways" abnormalities in smokers with a quantitative functional assessment such as that provided by cardiopulmonary exercise testing.

In this study, we will perform some of the purported tests of small airway disease (Berend 1983), such as phase III, closing volume and flows at low lung volumes (FEF_{25-75}) to fully characterize the volunteers studied.

Smoking and Bronchial Hyperreactivity:

Although the acute effect of cigarette smoke on airway reactivity is inconsistent, the effect of chronic smoking on increased bronchial hyperreactivity is well established. There is considerable information implicating inflammation as one of the factors responsible for this response (Wright 1992b, Griffith et al 1989).

The evaluation of airways hyperresponsiveness in smokers appears to be an important indicator of future outcomes. The "Dutch Hypothesis" suggests that airway hyperreactivity is an important predictor of an increased rate of decline in FEV_1 (Orie et al 1961, Rijcken et al 1988, Postma et al 1989, Sluiter et al 1991). The results of several epidemiologic and pathological studies have supported this hypothesis, suggesting that airway hyperreactivity could be a risk factor in the development of COPD (Ramsdell et al 1982, Taylor et al 1985, Sparrow et al 1987, O'Connor et al 1989). The same authors postulate that the lower the reversibility to inhaled bronchodilator, the higher the rate of decline in FEV_1 (Postma et al 1986, 1989, Anthonisen 1989). It appears that reversibility to inhaled bronchodilator and non-specific hyperreactivity are not necessarily parallel. COPD patients with no response to bronchodilator can show a considerable bronchoconstriction to methacholine challenge (Postma et al 1986). As part of the proposed work, airway reactivity will be evaluated in the smoker and non-smoker volunteers using a standard bronchial provocation challenge with methacholine. The degree of reversibility will be evaluated measuring the spirometric response to inhaled Albuterol.

The proposed work offers a unique opportunity to determine if the degree of reversibility and hyperreactivity of "normal" smokers could be a predictor of abnormal response to cardiopulmonary exercise testing. To our knowledge, this relationship has never been evaluated. Since the reversibility and hyperreactivity are indices of the host factor, the positive relationship between these measurements and the exercise performance would emphasize the role of the host factor in the development of cardiopulmonary abnormalities at an early stage before the development of COPD. Also, it would make more significant, the role of the cardiopulmonary exercise test as a potential discriminator of asymptomatic smokers who are at higher risk of developing full blown COPD.

Smoking and Cardiovascular Disease:

There is no doubt that smoking is also a significant risk factor in the development of cardiovascular disease. It is not surprising since tobacco smoke contains more than 4,000 components, many of them with harmful effects on the cardiovascular system. However, a direct causation mechanism linking specific components of cigarette smoke to the cardiovascular diseases has not yet been identified (Huber 1989, McGill 1988). Cardiovascular diseases are the most important causes of mortality in our society. Approximately 50% of all deaths in U.S. are due to cardiovascular disease (Brockie et al 1990).

The two major forms of cardiovascular disease associated with smoking are CHD and peripheral vascular disease, both of them mainly as a consequence of atherosclerosis and thrombosis (McGill 1988). The role that cigarette smoking plays in the pathophysiologic processes that result in myocardial infarction is not well understood. It appears that cigarette smoke works through reduction in plasma high-density lipoprotein cholesterol concentration, elevation in plasma fibrinogen and white blood cell count. In addition, smoking increases myocardial oxygen demand through increased heart rate and contractility with simultaneous decrease in myocardial oxygen supply, probably caused by adrenergically mediated alterations in coronary artery tone (McGill 1988, Belt 1990).

Patton and Vogel (1980) reported a significant incidence of coronary heart disease risk factors in a young otherwise healthy military population (17 to 35 years old). The incidence of obesity, elevated blood cholesterol and cigarette smoking were 29, 32 and 36%, respectively. Only 2.4% of the sample had ST-segment depression of 1 mm or greater during cardiac stress testing. The incidence of coronary heart disease risk factors in this young, physically active population is certainly impressive. However, these results are consistent with the findings of Enos et al. (1953), who reported that 70% of autopsied Korean war casualties who averaged 22 years of age had at least moderately advanced coronary heart disease. It is well known that due to the large cardiac reserve, a significant obstruction of the coronary arteries needs to be present to induce symptoms and ECG abnormalities. That explains why graded exercise testing (cardiac stress test) is not very sensitive in the early stages of the coronary heart disease.

In the proposed work, we will study an older group of asymptomatic smokers and non-smokers with similar levels of physical activity. By study design, subjects will have at least a 15 pack year smoking history which would be associated with a greater risk of CHD. We expect to uncover a higher incidence of occult heart disease in asymptomatic smokers using functional cardiac evaluations to include measurements of $\dot{V}O_2$, AT, O_2 pulse and HR-$\dot{V}O_2$ slope. The presence of occult heart disease could be one of the factors that explains the differences in $\dot{V}O_2$ max reported between smokers and non-smokers. This will be discussed in more detail in the next section.

Smoking and Exercise:

The effect of chronic cigarette smoking on exercise performance in asymptomatic subjects remains controversial. Although several investigators have shown consistent differences in exercise performance between smokers and non-smokers (McHenry et al 1977, Daniels et al 1984, 1986, Sue et al 1985), the results of these studies are tarnished by poor characterizations of the groups with respect to level of fitness, smoking histories, levels of COHb, concurrent conditions, abnormalities of resting PFTs, description of symptoms, etc.

Cooper et al (1968) studied the effect of cigarette smoking on endurance performance in 419 young (mean age = 19 years) Air Force recruits before and after basic training. Endurance field testing demonstrated significant differences in a 12 minute maximum running test and a more limited response to training over an eight week training period in the smokers compared to non-smokers. Endurance performance was inversely related to the number of cigarettes smoked daily as well as the duration of smoking. Aerobic capacity ($\dot{V}O_2$ max), $\dot{V}E$ max, and HR max were measured in only 47 subjects (25 non-smokers, 22 smokers) during a maximal treadmill exercise test. No significant differences in $\dot{V}O_2$ max or HR max between the 2 groups were observed. However, the authors do not mention if the distance run on the 12 minute test was the same or different between the small groups of smokers and non-smokers for whom $\dot{V}O_2$ data is available. Unfortunately, the limitations of this study include a smoking population with less than 5 years smoking history with no measurements of lung function (PFTs), and no measurement of carbon monoxide in the smokers. This last factor is important because of the apparent left shift of the HR - $\dot{V}O_2$ relationship for the smokers compared to the non-smokers. Such an effect could be a direct consequence of acute CO exposure from cigarette smoking and could provide an explanation for the disparity in exercise performance.

McHenry and co-authors (1977) studied 586 male members of the Indiana Police Force who were free of clinical cardiovascular disease. Subjects were divided in different groups according to the smoking habits. Shorter duration of maximal exercise testing in smokers vs. non-smokers was observed. In addition, smokers had higher maximal systolic blood pressure and lower maximal heart rate as compared to non-smokers during exercise. In the explanation of the differences, the authors did not take into consideration the lifestyle, resting PFT's, and the acute effect of COHb on the smokers.

The results of 2 large studies (n=763, n=685) carried out with Army personnel were reported by Daniels et al. (1984, 1986). These authors reported significant differences in maximal oxygen consumption between smokers and non-smokers which became more apparent as age increased. In one of the studies, they also reported that the 2 mile run time for smokers was longer than for non-smokers (1986). The 2 mile run test is used by the Army as a practical assessment of the level of fitness of its personnel. The authors postulate that besides smoking, the difference observed in these 2 studies could be partly attributed to differences in lifestyle. Unfortunately, the valuable data provided in these studies are available in abstract form only. In addition, the authors did not

consider the acute effect of increased CO in O_2 delivery to the exercising muscles of the smokers. Mello et al. (1988) demonstrated a very good correlation (r = -0.91 for males and -0.89 for females) between a maximal effort 2 mile run time and $\dot{V}O_2$ max. In contrast, Bahrke et al. (1986) did not observe a difference in the 2-mile running time between 50 military personnel smokers and 97 non-smokers. Smokers, however, performed less push-ups and sit-ups. The authors explained the lower level of muscular endurance in smokers to differences in lifestyles. However, it is uncertain why lifestyle differences would not also affect run times. This study is also limited by poor characterization of each of the groups. As part of our protocol, we will also measure the 2 mile running time to compare our results with previous studies and to have a simple test that would corroborate the results of the cardiopulmonary exercise testing. Correlation between the 2 mile run time and cardiopulmonary exercise testing results including abnormalities, airway reversibility, airway hyperreactivity, smoking history, and coronary heart disease risk factors, etc., will be determined. Significant relationships established between 2 mile run times and any of these factors may warrant a more complete evaluation for occult heart and/or lung disease. If helpful, such an approach could be modified for the civilian sector.

To determine the acute effect of smoking on exercise performance, Hirsch et al. (1983) studied 9 smokers on 2 different occasions, one during the smoking day (COHb levels of 6.6%) and one during the non-smoking day (COHb = 1.8%). They reported lower $\dot{V}O_2$ max, anaerobic threshold and O_2 pulse, but higher heart rate and systolic blood pressure at maximal exercise on the smoking day as compared to the non-smoking day. These data underscore the importance of measuring initial levels of COHb in studies which are primarily concerned with the chronic effect of smoking on exercise performance so that results are not obscured by the acute effect of CO.

Sue et al. (1985) reported the effects of smoking on exercise performance in asbestos-exposed workers. Smokers had lower $\dot{V}O_2$ max and O_2 pulse than non-smokers; a greater number of smokers had abnormal $P(A\text{-}a)O_2$ at peak exercise compared to non-smokers. One of the problems of this study is that it is difficult to determine the role played by the concurrent exposure to asbestos on the difference in exercise performance reported between smokers and non-smokers. In addition, other major problems of this work relate to poor patient characterization with respect to lifestyle, the number of subjects who were asymptomatic, the number of subjects with airway obstruction on PFTs and the number who were seeking disability. Also, this study did not evaluate COHb and the acute effect of CO exercise performance.

In a well designed and carefully conducted study, Frans et al. (1975) reported differences in pulmonary gas exchange during exercise between asymptomatic smokers (n=16) and non-smokers (n=14). The subjects were carefully characterized before the exercise tests with physical examination, chest X-ray, ECG, and PFTs. To avoid the acute effect of CO and nicotine, the smokers were instructed to abstain from smoking beginning the previous evening. However, COHb was not measured. The most consistent abnormalities detected in asymptomatic smokers during exercise were a reduction in diffusing capacity and an increase in $P(A\text{-}a)O_2$. The results of this study need

to be confirmed with more updated methodology.

We speculate that pulmonary gas exchange measurements could be one of the earliest detectors of cardiopulmonary abnormalities in asymptomatic smokers. The functional consequence of small airways inflammation and circulatory abnormalities could be ventilation perfusion mismatching, which would be manifested by increased $P(A\text{-}a)O_2$ and decrease DLCO during exercise. In the proposed work, we will measure pulmonary gas exchange during incremental exercise and will repeat the measurements during constant work so that incremental exercise gas exchange results are corroborated.

In summary, it appears that the majority of previous studies that have attempted to evaluate smoking and exercise have demonstrated some reduction in aerobic power and some pulmonary gas exchange abnormalities in smokers as compared to non-smokers. These differences could be explained by the presence of early pathology in the cardiopulmonary system. However, the inconsistencies and flaws of these studies, as noted previously, make the results and more importantly, their clinical application, limited. Many of the problems noted in previous studies will be avoided in the proposed work by carefully selecting, matching, and characterizing our asymptomatic smoker and non-smoker subjects. State of the art technology will then determine the effect of chronic smoking on the cardiopulmonary response to maximal exercise. Using an integrative approach, isolated measurements that were performed in different studies will be carried out in the same individuals and correlation of exercise results with those of extensive health questionnaire responses, PFTs, bronchial hyperreactivity results, tests of small airway function, etc., will be performed.

We anticipate that the study results will demonstrate subtle cardiopulmonary abnormalities in asymptomatic smokers vs. non-smokers which will allow a more convincing statement on functional physiologic abnormalities. We are optimistic that the results of our study will provide an effective early detection of cardiopulmonary abnormalities in asymptomatic smokers and possibly help identify a sub-population who would be at greater risk for the development of COPD and/or CHD. The sensitivity and specificity of the determination, however, would require validation in additional studies.

The diagnosis of early abnormalities can be a strong motivator for the involvement of smokers on cessation programs at a younger age. It is well established that the benefits of smoking cessation begin immediately, decreasing the risk of coronary heart diseases (McGill 1988). Although smoking cessation does not reverse the abnormal PFTs, it does normalize the rate of deteriorization of the pulmonary function of smokers similar to that of non-smokers. Smokers who quit before 40 years had FEV_1 levels similar to those who have never smoked (Higgins et al. 1993).

The tremendous importance of the early detection of cardiopulmonary abnormalities in smokers is underscored by the fact that only 15% of smokers develop COPD (DHHS 1984). The modulating effect of the host factor in the development of COPD in smokers is still unresolved and must be the topic of future studies.

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6. PLAN: (SEE ADDENDUM, PAGE 25)

a. Number of subjects: 120 (60 matched pairs of asymptomatic smokers and non-smokers).

b. Age range: 30-50 years of age.

c. Sex: Male.

d. Inclusion criteria for smokers and non-smokers:

- Age: 30-50 yrs.

- Health status: Asymptomatic (discerned from health questionnaire, see appendix) normal physical examination, spirometry (FVC, FEV_1 and FEV_1/FVC), CXR and ECG. ATS guidelines for interpretation of spirometry will be used (1987, 1991).

- Non-smokers - means less than 20 packs of cigarettes in a lifetime or less than 1 cigarette a day for 1 year.

- Smokers: Smoking history of at least 15 pack years.

e. Diagnostic criteria for entry: Normal physical examination, spirometry (FVC, FEV_1 and FEV_1/FVC), CXR and ECG. ATS guidelines for interpretation of spirometry will be used (1987, 1991).

f. Evaluations before entry: Medical records, medical history and physical examination, resting ECG and PFT (including bronchodilator challenge).

g. Exclusion criteria for smokers and non smokers:

- Known occupational exposure (i.e., asbestos).

- Clinical diagnosis of asthma (atopy, wheezing, eosinophil count > 500 m^3) (ATS 1987b).

- Response to inhaled bronchodilator (Albuterol) of more than 12% in FEV_1 and/or FVC from baseline values. ATS guidelines (1991).

- Abnormal response to PFT that purportedly evaluates small airways disease, i.e., flows at low lung volumes (FEF_{25-75}), volume of isoflow, and closing volume, will **NOT** be considered as a disqualifying condition.

- Intercurrent upper respiratory illness within 4 weeks of test data.

- In addition, higher risk assessment for coronary artery disease (discerned by health questionnaire, family history, and biochemical tests (cholesterol and lipid profile) will **NOT** be used as a disqualifying factor.

h. Source of subjects: Subjects from the Sergeants Major Academy from Fort Bliss, Texas will be recruited from the volunteers who agree to participate in this study after reading and signing the consent form.

i. Subject identification: The last 4 digits of the social security number will be used in the database to keep the confidentiality of the volunteers. A correlative number beginning with 1 will be arbitrarily assigned to each volunteer for the tables and graphs of the reports and papers that will be published with the results of the study.

j. Analysis of risks and benefits to subjects and risks to those conducting research:

(a) The literature indicates a death rate of approximately 0.5 per 10,000 clinical exercise tests in patients. In more than 70,000 maximal exercise tests performed in a preventive medicine clinic, no deaths were reported and only 6 major medical complications (ACSM 1991). The rate of medical complications in healthy, physically active, fit subjects is not known, but it appears to be extremely low. The exercise that the volunteers will perform are simulations of field activities that are routinely performed by soldiers.

(b) Benefits for the volunteers: The volunteers would gain knowledge of their level of aerobic performance (fitness).

(c) The only foreseeable risk for the personnel conducting the research is related to the accidental and extremely rare possibility of contamination with hepatitis B and HIV during the handling of blood samples, which will be reduced to a minimum, following the established guidelines for this procedure.

k. Precautions to be taken to minimize or eliminate risks to subjects and those conducting research: The Human Performance Laboratory is located within a well-equipped and fully staffed medical center with immediate access to all emergency services in event medical complication occurs. It is ideally suited for research conducted on human subjects. A crash cart is always available in the lab. One of the principal investigators (IMW), is an experienced board certified, pulmonary disease-critical care physician and ACLS/ATLS certified. Dr. Weisman will be present at all experimental sessions of the study. During the exercise tests, ECG and blood pressure will be monitored throughout. In case of any abnormal response to exercise the test will be discontinued immediately.

The Human Performance Laboratory has studied exercise performance in over 200 research volunteers over the last 8 years without incident related to procedures.

The use of gloves, goggles, and other established safety procedures will decrease the risks to a minimum for the researcher in charge, who will be obtaining blood samples.

l. Corrective action necessary if adverse reaction/incident occurs: If a medical problem occurs, the test will be discontinued immediately and the medical monitor will render appropriate care of the volunteer. If necessary, a crash cart is always available in the lab. Consultations from other sub-specialists may be sought. If necessary, the volunteer may be admitted to the hospital for medical care and follow up.

m. Special medical care or equipment needed for subjects admitted to the project: None.

7. EVALUATIONS MADE DURING AND FOLLOWING THE PROJECT: The study will be conducted in the Human Performance Laboratory, William Beaumont Army Medical Center, El Paso, TX at an altitude of 1,270 m mean P_B = 656 mm Hg and average temperature of 24° C. All the cardiopulmonary measurements, arterial blood gases and lactate analysis at rest and during exercise will be performed by Human Performance Lab personnel.

All blood samples will be properly discarded.

PROTOCOL (N=120)

SESSION	DAY 1	DAY 2
MORNING	EXPLANATION/CONSENT FORM --- PHYSICAL EXAM --- PFTs	PREPARATION --- MAXIMAL BIKE TEST
AFTERNOON	FAMILIARIZATION	CONSTANT WORK TEST

1st Day - Morning

- Protocol explanation and signing of consent form
- Completion of a cardiopulmonary questionnaire including smoking history and coronary risk factors (Appendix)
- Physical examination
- Smokers will be asked to refrain from smoking, starting 10 p.m. the night prior to testing, in order to wash out the CO from the body. The half-life of COHb, breathing room air, is 4 h. (Turino 1981).
- An expired gas sample for CO will be obtained to verify that COHb is less than 2%. In smokers, if higher, 100% O_2 will then be administered using a non-rebreathing mask for 1 to 2 hours; immediately following, another expired gas sample will be obtained and analyzed for COHb values. (CO analyzer, CMD/CO-1, Spirometrics, Maine).
- Pulmonary functions will be measured using a Pulmonary Function System (Sensor Medics 2200). The system utilizes a Mass Flow Sensor for measuring flow, a nitrogen analyzer for quantifying lung volumes (N_2 washout) and a carbon monoxide, methane and acetylene analyzer, for assessing diffusing capacity (single breath) ATS guidelines will be used to define normal values using 95% CI for spirometry (1987, 1991) and DLCO (1987c). The measurements will include:
  - Spirometry
  - Maximal flow volume loop at rest
  - MVV
  - Lung volumes including total lung capacity (N_2 washout)
  - Diffusing capacity
  - Closing volume and phase III (Single-breath N_2 test) (Berend 1983). This test is part of the standard menu that can be performed using the Sensor Medics 2200.

A conventional bronchial challenge will then be performed on each volunteer, using increasing concentrations of methacholine to evaluate airways hyperreactivity. Methodology and guidelines for interpretation will be those of the ATS (Cropp et al 1980)

and Hargreave et al (1985).

1st Day - Afternoon

- Exercise familiarization session: The volunteers will be asked to practice pedaling on the cycle ergometer while breathing through the mouthpiece connected to the cardiopulmonary measurement system. The modified Borg scale (Borg 1982) will be explained for quantification of physical effort, perception of breathlessness and muscle fatigue.
- Airways reversibility will be evaluated measuring the improvement in FEV_1 and FVC after administration of inhaled bronchodilator (Albuterol) (ATS 1991). Spirometry will be performed before administration of bronchodilator in order to assure baseline levels.

2nd Day - Morning

The objective of Day 2 morning exercise is to obtain cardiopulmonary and pulmonary gas exchange measurements during a standard incremental exercise test.

- Smokers will be asked to refrain from smoking beginning at 10 p.m. the night before.
- Preparation for the exercise test will begin with the placement of the ECG electrodes and blood pressure transducer for direct determination of blood pressure.
- An indwelling catheter will be placed in the radial artery prior to the exercise tests. The arterial line will enable the acquisition of blood samples for blood gas analysis (SaO_2, PaO_2, $PaCo_2$, pH), COHb, lactate, as well as the complete and accurate determination of pulmonary gas exchange including $P(A\text{-}a)O_2$, V_D/V_T, $P(a\text{-}ET)Co_2$. Our hypothesis is that subtle differences in gas exchange will be evidenced during exercise between smokers and nonsmokers. Arterial blood samples (3 cc) will be collected at rest, every other minute during exercise, and at minute 2 of recovery.
- Before the exercise test, an arterial blood sample will be obtained in smokers for COHb determination. If the value is higher than 2%, then 100% O_2 will be administered as described above.

Prior to the insertion of the arterial line, the Allen test will be performed to ensure that in case of complication with the radial artery, there is enough circulation through the ulnar artery to keep a normal blood flow to the hand. The patency of the arterial line will be maintained by continuous infusion of a commercial heparinized saline solution using a pressurized system. This methodology has been used successfully in our lab since 1983. The volunteers will be asked to perform a maximal incremental test to volitional exhaustion using an electronically braked cycle ergometer (Mijnhart KEM 3). The power will be increased by 25 W each minute, beginning with 3 min of unloaded pedalling (0 W). The duration of exercise will be approximately 8-10 min. Extensive cardiopulmonary measurements will be obtained including a dual functional assessment of the heart and lung. Power (W), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), respiratory exchange ratio (R), Minute Ventilation ($\dot{V}E$), Ventilatory equivalents for Co_2 ($\dot{V}E/\dot{V}CO_2$) and

O_2 ($\dot{V}E/\dot{V}O_2$), end-tidal pressure of O_2 ($PETO_2$), end-tidal pressure of Co_2 ($PETCO_2$), heart rate (HR), oxygen pulse ($\dot{V}O_2/HR$), tidal volume (VT) and breathing frequency (f) will be measured every minute before, during, and after exercise. Anaerobic threshold (AT) will be measured both non-invasively (ventilatory threshold) and by direct measurement of lactates (LAT) (Weisman et al 1992). VT/Vc and breathing reserve $\dot{V}E/MVV \leq 70\%$ will also be assessed. Breath-by-breath measurements (Beaver et al 1973) of the metabolic and cardiopulmonary variables will be obtained using a computerized system (Medical Graphics Corp 2001) which integrates flow (Pneumotachometer Hans Rudolph No. 3800) with respiratory gases, measured by a mass spectrometer (Perkin-Elmer, MGA - 1100). Heart rate and 12-lead electrocardiogram will be recorded with an electrocardiograph (Quinton 4000). Important relationships of $\dot{V}O_2$ vs. power, HR vs. $\dot{V}O_2$, O_2 pulse vs. power, $\dot{V}E$ vs. $\dot{V}O_2$ will also be obtained.

At the end of the test, subjective perception of exertion will be evaluated using the modified Borg scale (1982). Blood gases and pH will be analyzed in duplicate using an automated blood gas system (ABL 500, Radiometer, Copenhagen). Quality control will be assessed using tonometered blood samples and ATS blood gas guidelines (1985). SaO_2 and COHb will be determined in a spectrophotometric oximeter (OSM 3 Hemoximeter, Radiometer, Copenhagen).

Two hours for light lunch and rest will be allowed between the morning and afternoon exercise tests.

2nd Day - Afternoon

- The objectives of the afternoon exercise test are to measure the exercise tidal volume flow loop (Johnson et al 1991), and to validate the pulmonary gas exchange measurements (Furuike et al 1982, Zeballos et al 1991, 1991a) performed during the morning incremental exercise test. Our hypothesis is that some subtle differences may be observed in the tidal volume flow volume loops at peak exercise between smokers and nonsmokers reflecting possible early expiratory flow limitation not appreciated using other conventional methodology ($\dot{V}E$ max/MVV < 70%) and definitions of breathing reserve.
- A multistage constant work protocol will be used. The duration of each stage will be 4 min and the power will be increased 40 W with each stage. As in the morning test, the same metabolic and cardiopulmonary variables will be measured minute by minute at rest and during exercise.

At minute 3 of each stage, 3 to 4 tidal flow volume loops will be obtained and at minute 4 of each stage blood samples will be collected for pulmonary gas exchange measurements.

Tidal flow volume loops during exercise will be compared with a maximal flow volume loop performed at rest and immediately after exercise. The exercise tidal volume loops will be compared using end-expiratory lung volume as a reference, which will be determined by measurement of the inspiratory capacity immediately after the expiratory tidal volume loops have been obtained (Johnson et al 1991a). The subjects will be carefully coached (using an oscilloscope) for the performance of these maneuvers.

All the cardiopulmonary measurements, arterial blood gases and lactate analysis at rest and during exercise will be performed by Human Performance Lab personnel.

All cardiopulmonary data print outs, laboratory slips and health questionnaire responses will be kept in the volunteer's file. The database generated with all the results and the respective statistical analysis will be maintained by the principal investigator on a floppy disk and hard copy form.

The patient will be advised to report any unusual conditions that occur after completion of all exercise testing and departure from the laboratory. Such conditions will be reported to Human Performance Laboratory personnel; in the event they are not available and the situation requires immediate attention, emergency room visitation will be recommended.

Disposition of data: All cardiopulmonary data print outs will be kept in the volunteer's file. The database generated with all the results and the respective statistical analysis will be maintained by the principal investigator on a floppy disk and hard copy form.

Statistical Analysis: The calculation of the power sample size has been already explained. The SPSS/PC+ statistical program will be used for the analysis of the data, which will include descriptive statistics, Student t tests, Pearson correlation coefficients, and linear regressions. A level of $p < 0.05$ will be chosen for significance.

8. DEPARTURE FROM PROTOCOL FOR INDIVIDUAL PATIENTS: No modifications will be allowed.

9. INCIDENTS:

a. Definition: Pathological response to cardiopulmonary exercise testing and/or complications due to the indwelling arterial catheter that lasts more than 24 hours.

b. Immediate reporting: The Chief, Department of Clinical Investigation (or the DCCS) will be notified immediately by telephone, with the follow-up notification in writing (within 24 hours) of the circumstances surrounding the incident. Routine reporting - The Chief, Department of Clinical Investigation will be notified in writing within 24 hours of the circumstances surrounding the incident.

10. MODIFICATION OF PROTOCOL: Request for modification of the protocol, to include termination or extension, will be made in writing to the Chief, Department of Clinical Investigation.

11. USE OF INFORMATION AND PUBLICATIONS ARISING FROM THIS STUDY: The information obtained from this study will be published in peer review journals related to exercise, cardiopulmonary, and military specialties.

12. FUNDING IMPLICATIONS:

Personnel:	210,000
Equipment:	5,000
Consultant Services:	1,000
Supplies:	16,000
All Other Expenses:	500.00

	Total: 232,500

Funding for this project has been requested via VA Grant application pending approval.

13. HUMAN USE COMMITTEE: The WBAMC Human Use Committee will provide initial and continuing review.

MEDICAL MONITOR: LTC LARRY TREMPER, DEPT OF PEDIATRICS

14. DATE PREPARED: 28 June 1993

15. SIGNATURES:

Idelle M. Weisman, COL, MC, Director
Human Performance Laboratory, DCI

28 June 1993
Date

R. Jorge Zeballos, M.D, D.M.Sc.,
Human Performance Laboratory, DCI

28 June 1993
Date

Manuel Schydlower, M.D.
MANUEL SCHYDLOWER, COL, MC
Chief, Department of Clinical Investigation

July 23-93
Date

Addendum:

6. Plan:

a. Number of subjects: 120 (60 matched pairs of asymptomatic smokers and non-smokers). Sue's article (1985) "Lung function and exercise performance in smoking and non-smoking asbestos-exposed workers," was used as a reference to calculate the sample size for an expected change in mean $\dot{V}O_2$ in units of the common standard deviation. Using a 5% single-sided t test table in which $D = \delta/\sigma$ (Ostle), 60 would be the approximate number of subjects needed for each group with a 90% power. In order to obtain a similar life style and level of physical activity, the subjects will be recruited from the Fort Bliss Sergeant Majors Academy. The Sergeant Majors Academy trains approximately 500 senior enlisted army personnel every six months with an age range of 30-60 yrs, mean age = 40; 38% of them are smokers. In July, 1993, the Sergeant Majors Academy will be a 9 month course. There have been approximately 20 females in each of the last 4 classes. This means less than 5% of each class is female with a similar proportion of smokers. With such a small number of women, it would be impossible within this time frame (i.e., 2 years) to accede women on a volunteer basis into the study and have their data make a statistically meaningful statement.

b. Age range: 30 - 50 years of age.

c. Sex: male

N.B. - Subsequent studies involved in the validation of results from the present study would include other samples of asymptomatic smokers including females.

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority: 10 USC 3013, 44 USC 3101, and 10 USC 1071-1087.

Principle Purpose: To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

Routine Uses: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; adjudication of claims; and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.

Disclosure: The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may precludo your voluntary participation in this investigational study.

PART A(1) - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____, SSN _____.

having full capacity to consent and having attained my _____ birthday, do hereby volunteer/give consent as legal

representative for _____ to participate in _____

Early cardiopulmonary exercise abnormalities in asymptomatic smokers.

(Research study)

under the direction of COL Idelle M. Weisman, MC and Dr. R. Jorge Zeballos, M.D., D.M.Sc.

conducted at Human Performance Laboratory, William Beaumont Army Medical Center, El Paso, T

(Name of Institution)

The implications of my voluntary participation/consent as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

COL Idelle M. Weisman, MC

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights/the rights of the person I represent on study-related injury, I may contact

STAFF JUDGE ADVOCATE

at William Beaumont Army Medical Center, El Paso, TX 79920-5001 (915) 569-2280

(Name, Address and Phone Number of Hospital (Include Area Code))

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, I/the person I represent may be required (military volunteer) or requested *(Civilian volunteer)* to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my/the person I represent's health and well-being. My/the person I represent's refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

_____

PART A (2) - ASSENT VOLUNTEER AFFIDAVIT *(MINOR CHILD)*

I, _____, SSN _____ having full

capacity to assent and having attained my _____ birthday, do hereby volunteer for _____

_____ to participate in _____

_____

(Research Study)

_____

under the direction of _____

conducted at _____

(Name of Institution)

(Continued on Reverse)

WILLIAM BEAUMONT ARMY MEDICAL CENTER
HUMAN PERFORMANCE LABORATORY
HEALTH AND PHYSICAL ACTIVITIES QUESTIONNAIRE

1) Name:_____SSN#_____-_____-_____

2) D.O.B._____ Age_____ 3) Sex: M__F__

4) Unit:_____ 5) Work phone:_____

6) Race: White___Black___Oriental___Other_____

7) Marital Status: Single___Married___Separated___Divorced___Widowed___

8) What is highest grade completed in school?_____
(For example: 12 years is completion of high school)

9) Tobacco Smoking

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

IF YES TO A:

B. Do you now smoke cigarettes (as of 1 month ago)? — Yes___ No___ Does not apply___

C. How old were you when you first started regular cigarette smoking? — _____Age in years Does not apply____

D. If you have stopped smoking cigarettes completely, how old were you when you stopped? — ____Age stopped Still smoking____ Does not apply____

E. How many cigarettes do you smoke per day now? — ___Cigarettes/day Does not apply____

F. On the average of the entire time you smoked, how many cigarettes did you smoke per day? — ____Cigarettes/day Does not apply____

COUGH

10) A. Do you usually have a cough? (Count a cough with first smoke or on first going out-of-doors. Exclude clearing your throat.) — Yes___ No___

B. Do you usually cough as much as 4 to 6 times a day, 4 or more days — Yes___ No___

C. Do you usually cough at all on getting up, or first thing in morning? — Yes___ No___

D. Do you usually cough at all during the rest of the day or night? — Yes___ No___

IF YES TO 10A, 10B, 10C, OR 10D, ANSWER QUESTIONS 10E, 10F AND 10G. IF NO TO ALL, SKIP TO QUESTION 11.

E. Do you usually cough like this on most days for 3 consecutive months or more during the year? Yes___ No___

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

G. Do you have episodes of coughing with exercise? Yes___ No___

PHLEGM

11) A. Do you usually bring up phlegm from your chest? (Count phlegm with the first cigarette or on first going out-of-doors. Exclude phlegm from the nose. Count swallowed phlegm.) **If No, skip to Question 11C.** Yes___ No___

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

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

D. Do you usually bring up phlegm at all during the rest of the day or at night? Yes___ No___

IF YES TO QUESTIONS 11A, 11B, 11C, OR 11D, ANSWER QUESTIONS 11E AND 11F. IF NO TO ALL, SKIP TO QUESTION 13.

E. Do you bring up phlegm like this on most days in 3 consecutive months or more during the year? Yes___ No___

F. For how many years have you had trouble with phlegm? _____no. years

EPISODES OF COUGH AND PHLEGM

12. A. Have you had periods or episodes of increased cough and phlegm lasting for 3 weeks or more each year? Yes___ No___

13. Does your chest ever sound wheezy or whistling?

A) With a cold? Yes___ No___

B) Occasionally, apart from colds? Yes___ No___

C) Most days and nights Yes___ No___

D) After or during exercise Yes___ No___

E) Have you ever been diagnosed as having asthma? Yes___ No___

IF THE ANSWER TO 13E IS YES, ANSWER F - H, OTHERWISE GO TO 13I:

F) Do you still have it? Yes___ No___

G) Was it confirmed by a doctor? Yes___ No___

H) At what age did it start? ____ age in years

I) If you no longer have it, at what age did it stop? ____ age in years

J) Do you currently receive medication or treatment for asthma? Yes___ No___

PAST ILLNESSES-LUNG

14. Did you have lung trouble before age 16? Yes___ No___

15. A) Have you had attacks of bronchitis? Yes___ No___

B) Was it confirmed by a doctor? Yes___ No___

C) At what age was your first attack? ____ age in years

16. A) Did you have hay fever? Yes___ No___

B) Was it confirmed by a doctor? Yes___ No___

C) At what age did it start? ____ age in years

17. Is there a family history:
Chronic bronchitis Yes___ No___
Emphysema Yes___ No___
Asthma Yes___ No___

CARDIOVASCULAR DISEASE

18. Have you ever had chest pain or shortness of breath with exercise? Yes___ No___

19. Have you ever had a cardiac stress test? Yes___ No__

If yes, why? _____
when? _____
results? _____

20. A) Do you have hypertension (blood pressure greater than 145/90)? Yes___ No___

B) Are you on medication? Yes___ No___

C) If yes, what medications? _____
_____

21. Is there a family history of heart disease? Yes___ No___
stroke? Yes___ No___
hypertension? Yes___ No___

22. A) Do you have diabetes? Yes___ No___

B) If yes, are you on medication? Yes___ No___
diet controlled? Yes___ No___

C) Is there a family history of diabetes? Yes___ No___

23. A) Do you have high cholesterol (greater than 200 mg/dl) Yes___ No___

B) If yes, are you on medications? Yes___ No___

C) What medication? _____

D) Is there a family history of high cholesterol? Yes___ No___

24. A) Is your mother living? Yes___ No___

B) If no, cause of death? _____

C) Is your father living? Yes___ No___

D) If no, cause of death? _____

PHYSICAL ACTIVITY

25. A) When was the last time that you took a PT Test? Mo___ Yr____

B) Did you pass the APFT? Yes___ No___

C) What was your time for the 2 mile run? _____min

D) What was your total score (run, push-ups, sit-ups)? _____points

E) What is your weight? _____lbs

F) Do you meet Army weight requirements? Yes___ No___

G) What is your height? _____inches

26. In the past 3-6 months, how would you describe your level of physical activity? Very Active____
Active_____
Less Active____

27. How often do you engage in: running ____times per week
calisthenics? ____times per week
weight lifting? ____times per week

28. In addition to army requirements, do you regularly play basketball_____, baseball_____, soccer_____, cycle_____, other_____?

OCCUPATIONAL EXPOSURE

29. What is your MOS? _____

30. What has been your primary job occupation during your life? _____

31. Have you had exposure to

asbestos____
welding_____
toxic chemicals____
which one(s)?_____