increased platelet stickiness and aggregation, pointing to a potential role in coronary disease. There is some evidence that these physiological effects may be dose related and somewhat diminished with lower nicotine varieties of cigarettes.

5. Carbon monoxide has a negative inotropic effect on the myocardium of patients with angina pectoris. When combined with hemoglobin in the form of carboxyhemoglobin, carbon monoxide may increase the permeability of the blood vessel walls to lipids, thereby promoting atherosclerosis.
6. Cigarettes with unperforated filters yield lower "tar" and nicotine levels than unfiltered cigarettes, but they yield more carbon monoxide than do unfiltered cigarettes at the same "tar" yield. Carbon monoxide yields are lower in cigarettes with perforated filters, but as the composition of cigarettes has changed, carbon monoxide yields have decreased much less in proportion to the decrease in "tar" and nicotine yields.
7. In studies of patients with angina pectoris, increased carboxyhemoglobin levels significantly shorten exercise time until the onset of angina pectoris.
8. Myocardial ultrastructural changes have been found in rabbits exposed to carbon monoxide.
9. Most cardiovascular studies have focused on nicotine and carbon monoxide rather than on "tar," which has not been shown to have a major acute role in cardiovascular disease. Even less is known about other constituents of cigarette smoke.
10. Not all cigarettes that produce a lower yield of one substance necessarily provide a lower yield of other substances.
11. Evidence on the association between CHD and filter cigarettes is somewhat conflicting. One major study showed a reduction of 10 to 20 percent in coronary deaths among persons smoking lower "tar" and nicotine cigarettes as compared with those who smoked higher yield cigarettes, but other surveys have shown a slightly increased risk of coronary mortality in people who smoked filter cigarettes relative to those who smoked nonfiltered cigarettes. Recent unpublished data from the Framingham Study do not show a lower CHD risk among smokers of filter cigarettes.

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Section 5. CHRONIC OBSTRUCTIVE LUNG DISEASE

CONTENTS

The Research Problem

The causal relationship between cigarette smoking and chronic obstructive lung disease (COLD) (chronic bronchitis and chronic obstructive pulmonary emphysema) is well documented (*34*). However, the possible differences in the effects of higher versus lower "tar" and nicotine cigarette smoke in the pathogenesis of chronic obstructive lung disease are not known. COLD usually progresses slowly; physiologic and pathologic abnormalities may exist for an extended period of time prior to the development of disabling clinical manifestations. The latter are usually associated with severe lung damage or destruction. It is uncertain which of the many ingredients in cigarette smoke has a role in the production of COLD. Lower "tar" and nicotine cigarettes may have no impact, or indeed an untoward impact, on the development of COLD. Therefore, it is urgent that research be carried out to resolve this complex problem.

Cigarette-related chronic lung disease may be subdivided into three major components: (1) uncomplicated chronic bronchitis, a disease of mucous hypersecretion and cough; (2) chronic bronchitis and bronchiolar inflammation, similar to (1) but with airflow limitation caused by intrinsic airway pathology; and (3) emphysema, a disease associated with anatomical hyperinflation of the distal air spaces and destruction of lung parenchyma. Because cigarette smoking is associated with all of these conditions, they commonly coexist. The factors causing one or more of these diseases to develop in response to cigarette smoke in some individuals and not in others are unknown. Cough and mucous hypersecretion are common symptoms among cigarette smokers, while evidence of airflow limitation is significantly less common. Recent evidence suggests that the early stage of emphysema is associated with cigarette smoking-related inflammation in airways less than two millimeters in diameter (*11*).

Research on the response to inhaled irritants is usually focused on one or more of the anatomical components of the lung: the airways, the cellular and biochemical contents of the alveolar spaces, and the contents and structure of the alveolar septa or interstitia. Responses in the airways may consist of alterations in epithelial cell types, mucous gland hyperplasia, hypersecretion of mucus, inflammation, impairment of mucociliary function, abnormalities of immunologic factors or other substances, smooth muscle hyperreactivity and hypertrophy, and intrinsic narrowing fibrosis or destruction of small airways. Physiologic responses reflect airflow limitation, early closure of small airways, and nonuniform distribution of inspired air.

In the alveolar spaces, free cells (including alveolar macrophages and neutrophils), surfactant (a phospholipid secreted by the alveolar lining cells), enzymes released or secreted by macrophages or neutrophils, and protease inhibitors and other proteins that reach the alveolar spaces by transudation from the circulation are all under study. The alveolar

septum or interstitium, consisting of alveolar lining cells, basement membrane, capillary endothelial cells, other alveolar interstitial cells, and the connective tissue framework composed primarily of collagen, elastin, and proteoglycans is the focus of much research. Physiologic alterations reflect decreased surface area for gas exchange and alterations in the elastic recoil of the alveolar structures.

The lung plays an active role in the production and metabolism of various bioactive substances such as angiotensin, prostaglandins, and serotonin. This anatomically, physiologically, and biochemically complex organ is exposed to the external environment and its agents, including cigarette smoke and air pollution. Complicating host factors also affect this system: age; sex; inherent reactivity of the airways; genetic factors that predispose to emphysema, such as alpha$_1$-antitrypsin deficiency; childhood infections; and as yet undefined familial factors.

The design of experiments to determine the short- or long-term effects of cigarettes on smokers is made difficult because the composition of cigarettes and the population of smokers have been changing over the past 10 to 15 years. Further complicating this problem is the large number of tobacco smoke components with varying solubility and interactive capabilities. There is also a lack of knowledge of the topography of cigarette smoking. Individual differences in the mechanics of smoking such as the volume of puff, holding time in the oral cavity, depth of inhalation, time of retention in the lung, and length of butt significantly influence the composition, distribution, penetration, and retention of cigarette smoke components in the lungs. The topography of smoking may vary depending on the nicotine content. The composition and concentration of the gas phase components that reach the small airways and alveoli may have a significant role in the production of emphysema, while the particulate matter that deposits in the larger airways may be more involved in the development of chronic bronchitis. The target tissues, cells, or ultrastructural components may be different in chronic bronchitis and emphysema. Thus it is extremely important to develop a better understanding of the topography of smoking so that appropriate experiments can be designed to determine dose-response relationships of pertinent smoke components and the reactions to them in the different regions of the lung. The problem is that of assessing the effects of continually changing cigarette products on a continually changing population of smokers. The ultimate concern is for the effects on smokers. For chronic lung disease, this effect can best be assessed by the combination of epidemiologic evaluations of populations at risk and laboratory evaluations of the effects of smoke on the mechanism of disease production.

Current Research Findings

Recent advances in research have led to a plausible hypothesis for the etiology of pulmonary emphysema: If an imbalance between endogenous elastolytic enzymes and protease inhibitors in the lungs permits active enzymes to exist in the alveoli or alveolar walls, degradation of the alveolar tissue components, primarily elastin, will occur (*25, 26*). The sources of endogenous elastase are polymorphonuclear leukocytes and alveolar macrophages. The major source of the inhibitor is the serum protein, alpha$_1$-antitrypsin, which reaches the alveolar space by the process of transudation. This hypothesis is reinforced by experimental data from a variety of sources. Humans with a genetically transmitted deficiency of alpha$_1$-antitrypsin are prone to develop emphysema (*29*). The instillation of elastolytic enzymes into the lung, including human neutrophil elastase, will produce experimental emphysema in animals (*33*). Cigarette smoke is implicated in this process by mechanisms that may lead to the development of emphysema.

Alveolar macrophages from smoke-exposed mice increase in number and secrete significantly greater amounts of elastase than macrophages from control mice (*35*). Human alveolar macrophages from cigarette smokers also secrete significantly more elastase than macrophages from nonsmokers (*32*). Alveolar macrophages exposed to cigarette smoke produce a chemotactic substance for polymorphonuclear leukocytes (*17*). Mild exposure to cigarette smoke also increases the release of elastase from human polymorphonuclear leukocytes (*5*).

Cigarette smoke inhalation decreases the alpha$_1$-antitrypsin activity in the rat lung (*22*), and alveolar lavage from human smokers shows a functional antiprotease deficiency (*16*). This effect of cigarette smoke on alpha$_1$-antitrypsin is related to its oxidant effect (*1, 8*). The loss of inhibitory activity of alpha$_1$-antitrypsin is induced by oxidation of methionine residues at the reactive center of the molecule (*23*). A chemical oxidant, chloramine-T, administered to dogs, also induces a reduction in the elastase inhibitory capacity of both the serum and alveolar lavage fluid, and the animals develop morphologic changes of mild emphysema (*13*). This animal model simulates the human alpha$_1$-antitrypsin deficiency state except that the deficiency is functional and not in absolute quantity. Oxidants are also released when polymorphonuclear leukocytes are exposed to exogenous elastase (*27*).

This *in vivo* and *in vitro* experimental evidence indicates that cigarette smoke both increases the amount of elastase in the alveolar tissue or air spaces and simultaneously reduces the functional capacity of the primary elastase inhibitor, alpha$_1$-antitrypsin, and links the action of cigarette smoke to the possible production of disease in humans. Although there is general acceptance of the protease-inhibitor imbalance hypothesis, it has yet to be directly related to human emphysema. There are no available studies in which smoke from

regular and lower "tar" and nicotine cigarettes has been used to determine if there are differences in their effects on elastase or oxidant release or production, or concentrations of cigarette smoke oxidants that could affect the functional capacity of alpha$_1$-antitrypsin.

Small airway inflammation and bronchiolar inflammation develop much more frequently in smokers than in nonsmokers (*11*). Findings in the lungs of individuals 40 years of age or older who died suddenly of nonrespiratory causes revealed inflammation, increased numbers of goblet cells, and muscular hypertrophy in small airways. There was also an increase in airways under 400 microns in diameter and in the occurrence of respiratory bronchiolar inflammation in the smokers. The lungs showing both the largest number of small (under 400 microns) airways and the most airway pathology had the most centrilobular emphysema, the predominant type found in cigarette smokers. The respiratory bronchiolar inflammation was characterized by infiltration with macrophages that extended into adjacent alveolar walls. Previous studies of resected lung from smokers showed that the severity of similar small airway pathology in excised human lungs correlated with impairment in ventilatory function (*10*). The small airway disease and severity of emphysema also correlated with changes in small muscular pulmonary arteries that could be important in the development of pulmonary hypertension (*19*). These studies suggest that cigarette smoke produces small airway pathology, which is a factor in ventilatory function impairment. The respiratory bronchiolar inflammation may initiate an enzyme-inhibitor imbalance in the centrilobular regions. The release of elastase from alveolar macrophages and from neutrophils brought to the alveoli by increased chemotaxis and the impairment of alpha$_1$-antitrypsin function could be stimulated by cigarette smoke in the alveolar spaces. This leads to destruction of alveolar wall elastin and then to the morphologic and physiologic changes observed in emphysema.

The oxides of nitrogen occur at relatively high levels in cigarette smoke and at lower levels as an ambient air pollutant. Exposure of dogs to NO_2 and NO for 68 months resulted in pulmonary function changes characteristic of emphysema (*18*) that continued to progress after cessation of exposure. Long-term exposure to oxides of nitrogen results in airway and alveolar epithelial changes and parenchymal damage that suggest an emphysema-like disease (*14*). Evidence suggests that the damage is induced by an oxidant-type mechanism. In addition, the most severely affected tissues are the terminal bronchioles, alveolar ducts, and adjacent alveoli, which are infiltrated with inflammatory cells. The latter are primarily macrophages with other mononuclear cells and occasional granulocytes. Interruption and thickening of elastic fibers in alveolar walls were observed. These lesions are similar to those induced by cigarette smoke and suggest

that the oxides of nitrogen may be one of the agents responsible for the initiation of the early lesions of human emphysema.

As an outgrowth of the elastase-inhibitor imbalance hypothesis for the etiology of emphysema, new potential markers or indicators of disease are being investigated. Since lung elastin appears to be the target substance for degradation, several laboratories are seeking a method to identify products of elastin breakdown that would serve as markers for the development of emphysema. In one study, peptide breakdown products of lung elastin were identified in the serum of dogs in which experimental emphysema was induced by the administration of elastase (*28*).

Other investigators are measuring the urinary excretion of desmosine, the cross-linking amino acid of elastin that appears as a breakdown product. If it can be demonstrated that elastin degradation products are significantly elevated in the blood or urine of smokers who have early emphysema, undetectable by other means, further development and refinement of such tests may provide a sensitive biochemical marker or screening test for the early detection of emphysema. Such a measurement would simplify cross-sectional and other epidemiologic studies in which the results in subjects who smoke regular cigarettes could be compared with those of subjects who smoke lower "tar" and nicotine cigarettes.

Studies of acute human responses to the different types of cigarettes, which may be important in the pathogenesis of chronic lung disease, are beginning to appear. The type of cigarette and the amount of smoke inhaled into the lungs, measured by changes in blood nicotine level or carboxyhemoglobin level, are not related to the occurrence of acute airway responses to smoke inhalation (*21*). The authors found that individual susceptibility is a factor, but even more important is the smoking pattern. Holding the smoke in the mouth prior to inhalation into the lungs reduced the response, whereas direct inhalation from the cigarette into the lungs caused an increased number of smokers to develop spirometric changes indicative of bronchoconstriction. This was independent of "tar" yield and reinforces the importance of the cigarette smoking pattern in the dose-response relationship. The study showed that the habitual cigarette smoker avoids the direct irritant effect of cigarette smoke by temporarily storing the smoke in the mouth before inhaling it into the lungs and also demonstrated that the smoke inhalation pattern is important in determining the relevant concentration of the constituents of smoke that reach the lungs.

There are few epidemiologic studies, either cross-sectional or longitudinal, that deal with differences relating to the "tar" and nicotine yield of cigarettes smoked. In a survey of over 18,000 civil servants (*20*), the "tar" yield and the number of cigarettes smoked daily were correlated to respiratory symptoms and spirometry. Sputum

production and air flow obstruction increased as cigarette consumption increased. "Tar" yield influenced sputum production, but not the degree of air flow obstruction. When subjects smoking lower "tar" cigarettes smoked over 20 per day, their sputum production was the same as that of the higher "tar" cigarette smokers. In this study of asymptomatic men, the air flow obstruction was related to the daily cigarette consumption. Higher "tar" cigarette smokers did not have a greater air flow obstruction than those using lower "tar" cigarettes. If there was a compensating increase in the number of cigarettes smoked by the smokers of lower "tar" and nicotine cigarettes, the advantage of reduced mucous hypersecretion was lost. Ex-smokers had better lung function than current smokers with comparable total cigarette consumption. The authors conclude that mucous hypersecretion depends on the "tar" fraction of the cigarette's smoke and that the development of air flow obstruction depends on the number of cigarettes smoked. They reason that the gas phase of the smoke, particularly the volatile compounds, was responsible for damage leading to air flow obstruction. They hypothesize that "tar" droplets and soluble gases, such as sulfur dioxide and hydrogen cyanide, are more likely to be deposited or absorbed in the larger bronchi where mucus is produced. The smaller bronchi, which are the site of airway obstruction, and the alveoli are exposed to a lower concentration of "tar," but to a full concentration of insoluble gases, such as the nitrogen oxides and ozone. Higenbottam and co-workers (*20*) did not differentiate between emphysema and chronic bronchitis as a cause of airway obstruction. The authors conclude that smokers of lower "tar" cigarettes who compensate by smoking more cigarettes or inhaling more deeply may increase the risk of obstructive airway disease. They suggest that more information is needed about the nature and concentrations of irritants in the gaseous phase of smoke and their relation to concentrations of "tar" and respiratory damage.

Another British study (*15*) indicates that filter cigarette smokers report less cough. The difference between the groups of smokers was relatively small, however, and the filter cigarettes that were smoked are probably dissimilar to those currently smoked in this country. Dean et al. (*12*) reported the results of two retrospective studies, separated by an interval of 10 years but carried out in the same area, to determine whether the increasing use of filter cigarettes produced less risk of dying of four diseases, including chronic bronchitis. In the second study, relatives of those who had died were interviewed to obtain the information about the smoking habits of the deceased individuals. The cause of death was determined from death certificates. A living population was selected as the control sample. The investigators found that mortality from chronic bronchitis was related to age, to the number of cigarettes smoked, and to the level of inhalation. The estimated risk of mortality from chronic bronchitis of

the population who smoked filter cigarettes since 1954 was about half that of the continuing regular cigarette smokers. Many features of this study could cause bias or misinterpretation: information was collected from relatives of deceased individuals; the information on the living and the deceased populations related to different points in time; and changes in air pollution levels and in the population probably occurred during the period of the study. From the epidemiologic standpoint, firm conclusions cannot be drawn from this study.

In an ongoing study of a healthy population, the rates of decline of pulmonary function in smokers and nonsmokers show only a very small difference (*6*). However, 8 to 12 percent of smokers have a distinctly more rapid decline in the FEV_1. These are primarily male smokers and may represent the group who will ultimately develop symptomatic obstructive lung disease. In the entire population, the tests of "small airway function," such as closing capacity, show no difference in the rate of change between smokers and nonsmokers. These tests tend to be abnormal in those individuals who develop an abnormal FEV_1, but at the same time, a large number of subjects with abnormal tests of small airway function will not develop a rapidly decreasing FEV_1. Data about differences in the type of cigarettes smoked were not obtained, but the extremely small difference between healthy smokers and nonsmokers, except for the small group of rapid decliners, suggests that studies of large populations with this objective may not be revealing.

Another longitudinal study suggests that a study of approximately 8 years is necessary to identify those asymptomatic smokers who will show a significantly accelerated rate of lung function deterioration (*15*). This study also finds that, in spite of frequent smoking-induced cough and expectoration, only a relatively small percentage of smokers show a greater than average decline in respiratory function. The authors report that when a group of asymptomatic middle-aged smokers who had subnormal FEV_1 levels and rapid decline stopped smoking, the rate of deterioration reverted to that of nonsmokers although there was no significant improvement in the initially determined abnormal lung function. This study did not distinguish between the effects of lower "tar" and nicotine and regular cigarettes.

The traditional tests of airflow limitation such as FEV_1 are thought to reflect changes relatively late in the course of disease. Some investigators have demonstrated that flow measurements taken from the near terminal part of the forced vital capacity tracing are more sensitive, but these are not widely used to date (*30*). Newer tests of small airway function such as slope of phase III, closing capacity, and volume of isoflow with helium and oxygen have not been established for their specificity in indicating the development of significant chronic lung disease (*4*).

A study carried out in two successive decades, in which successively autopsied airways from lungs of smokers were studied for bronchial epithelial changes, demonstrated a decrease in changes thought to be related to carcinogenesis (*2*). This favorable change was thought to be related to the increasing use of lower "tar" and nicotine cigarettes. Unfortunately, this study did not examine the lungs for evidence of chronic obstructive lung disease.

Future Research Approaches

Animal models in which emphysema has been induced by elastolytic enzymes have been reported by a number of authors (*24*), but for reasons that may reflect a combination of factors, such as the shorter life span of animals, the method of smoke exposure, and species resistance, there are no published studies that acceptably show in an animal model that the development of emphysema is induced by cigarette smoking. Thus, a successful animal model has not been developed in which the relationship of different types of cigarettes to the development of emphysema can be studied. One study in which dogs received smoke directly through chronic tracheotomies reported the development of emphysema (*3*). The lesions were not conclusive and the results have not been confirmed by others. Therefore, to elucidate more clearly the differences between regular and lower "tar" and nicotine cigarette smoke exposure, it will be necessary to study other aspects of lung function, either biochemical or physiological, that may be altered by the cigarette smoke and that are projected to be important pathogenetic mechanisms in humans.

As suggested in the preceding paragraphs, much new information will be needed before conclusions can be drawn about the effect of lower "tar" and nicotine cigarettes on the development of COLD. Acute and subacute responses could be measured by physiologic studies, although such responses may not be relevant to the development of chronic, irreversible lung disease. The quantity and composition of mucus secreted in the airways in response to different types of cigarettes may be studied in animals or humans. The histology of the bronchial mucosa may be evaluated in human material from lobes or lungs resected for other reasons, from biopsy specimens, or from post mortem findings in which changes related to chronic bronchitis or emphysema are specifically quantitated. In autopsy or resected lungs from smokers of regular and of lower "tar" and nicotine cigarettes, factors in the small airways such as lumen size, number of airways, cell types, goblet cells, muscle hypertrophy, and inflammation may be evaluated. Enzyme inhibitors produced in the tracheobronchial tree could also be evaluated, as could the secretion of immune globulins. Effects of cigarette smoke on the mucociliary function of the bronchial mucosa is another potential measurement.

The response of the alveolar region of the lung could be determined by biochemical, morphologic, and physiological techniques. The cellular content of the air spaces, the functional status of alpha$_1$-antitrypsin, the presence of chemotactic factors, oxidant production by neutrophils or macrophages, elastase production and inhibition, and degradation products of lung elastin may be measured in response to smoke exposure. Human studies would require bronchioalveolar lavage to obtain these data, although the invasive nature of this technique may preclude its use in large populations lacking other indications. Production and turnover rates of lung elastin and collagen, the numbers and types of interstitial cells, and the presence of free or bound elastase may be evaluated in the interstitial tissue. Macrophage and neutrophil responses to the whole smoke and selected fractions can be investigated. These include phagocytosis and elaboration of elastases, chemotactic factors, and oxidants. Surfactant production and alterations might be evaluated. Many of these factors are deemed important in the determination of the protease-antiprotease balance in the lungs. The development of some measurements into standard biologic assays by which the various types of cigarette smoke may be evaluated would be a valuable advance. This research would not only aid in the development of techniques to assess the response to various types of smoke, but also would add important information to our knowledge of the pathogenesis of disabling chronic obstructive lung disease in humans. Physiologic measurements of lung volumes, elastic recoil, and diffusing capacity of the lungs may be studied in humans and animals, although in published studies to date, the observed effect is minimal or negative.

The question of which fraction of cigarette smoke contains the agent(s) that alter the lung defense mechanisms to induce chronic lung disease must be resolved. It is not feasible to evaluate each of the several thousand substances in cigarette smoke, but the major fractions that contain the offending agents and the distribution and penetration of these fractions should be studied. Gas phase constituents should be evaluated by category, and the method of exposure must be related to the actual smoking habits of humans. Cigarette smoking-machines that produce 35 ml puffs and the techniques by which animals inhale cigarette smoke in research models may not be representative of the human situation. Research techniques must be devised by individuals who are knowledgeable in the field of aerosol distribution and deposition, in the chemistry of cigarette smoke, and in the biophysics of the distribution of smoke in the airways. Patterns of inhalation for the average smoker must be studied in more detail. If individuals who switch from regular to lower "tar" and nicotine cigarettes undergo a change in smoking pattern, such as deeper or more frequent puffs, this must be taken into consideration because the contents of the smoke, the size of the particulate matter, and the distribution of smoke in the lung may change with the variations in

inhalation patterns. Such information must be applied to dosimetry in short-term *in vivo* and *in vitro* experiments as well as in epidemiologic or population studies.

Epidemiologic Studies

Studies of populations of smokers with well-defined smoking histories are a major tool in determining whether a real difference exists between smokers of regular cigarettes and smokers of lower "tar" and nicotine cigarettes. If, in well-planned epidemiologic studies, there is no difference found in the human occurrence or severity of chronic obstructive lung disease between smokers of different types of cigarettes, more basic research involving humans, animals, or *in vitro* systems to determine differences between the effects of smoke products would be less useful.

The design of epidemiologic research for this purpose raises a number of issues. Determining the true dose of smoke in cross-sectional, retrospective, or prospective population studies is a difficult problem. Most studies rely on patient histories to obtain dosage information. The accuracy of recall, the design of the questionnaire, and the skills of the interviewer all influence the accuracy of smoking history. The cigarette itself presents a problem in studying the significance of the lower "tar" and nicotine brands because changes in the content and design of cigarettes have continued over the past 10 to 15 years. This "moving target" makes evaluation of the dose-response in populations difficult, especially since a large proportion of current smokers began their smoking careers with regular cigarettes and switched after varying periods of time. The comparison of mortality rates is a commonly used epidemiologic tool. There are well-known problems in obtaining accurate mortality data on chronic lung disease, particularly in retrospective studies in which death certificates obtained 10 or more years ago are utilized. Morbidity, including hospital days and days lost from work because of respiratory illnesses, might also provide useful information but is limited because of the selective nature of populations (*31*).

Population studies that investigate the rate of decline of lung function proportionate to the number of cigarettes smoked have shown variable results. Most of the available data apply to smoking without regard to cigarette yield. Environmental factors such as air pollution may change simultaneously, and corrections must be made for these factors.

The mean differences between the rate of decline of the FEV_1 in populations of nondiseased smokers and nonsmokers are very small. A difference between the smokers of higher and of lower "tar" and nicotine cigarettes may be impossible to detect. However, the subgroup of the smoking population that shows a more rapid decline should

receive special attention, since it is probable that this group of smokers, for reasons yet unknown, is most likely to develop significant disease. Random variations from year to year in the measured FEV_1 in individual patients require an extended period of time before valid data can be obtained (*7*). Biochemical tests that may serve as new markers for chronic lung disease are in the early research stage and should be explored as soon as possible. Under the best of circumstances they could replace the physiologic tests that measure air flow limitation as the earliest practical mechanism to detect lung damage. These measurements should be given high priority to determine their ultimate usefulness. In the meantime, it would be reasonable to collect and store for future use blood and/or urine samples from the screened populations.

The lack of specific, detailed information about the human dose-response to cigarette smoke and the mechanism that causes individual susceptibility to more rapid deterioration of lung function results in difficulty in predicting sample size and the length of time needed for a population study to determine differences between the smokers of higher and of lower "tar" and nicotine cigarettes. Current data suggest that the time and effort required to mount new epidemiologic studies may delay the acquisition of needed information. However, there are several ongoing studies in which epidemiologic data, both cross-sectional and longitudinal, are being collected with relevance to chronic lung disease. It is appropriate to consider the utilization of these current studies where populations are already identified. Data on the history of brands smoked could be added. Available information about the "tar," nicotine, and carbon monoxide yield of the various brands offers one measure of dosage. A recently developed radioimmunoassay for plasma nicotine levels may also be a helpful tool (*9*), although smoking patterns may be as important as the number of cigarettes smoked in determining the actual dosage.

Additional questionnaire material involving brand data and history of morbidity related to respiratory symptoms could be superimposed on ongoing studies. The accuracy of historical data on cigarette smoking must be verified to the best possible extent. If new indicators serving as a screening test, such as blood or urine analysis for lung elastin degradation products, become available, they should be incorporated into the studies. Depending on their diagnostic reliability, it might be possible to study a considerably smaller population than that required for studies of morbidity, mortality, and lung function deterioration. All studies yet to be initiated should include questions on brand history. This would require the revisions in the standard questionnaires of the American Thoracic Society and Medical Research Council of Britain. An ideal longitudinal study will require the enrollment of younger subjects who begin their smoking careers with regular or with lower "tar" and nicotine cigarettes and continue to smoke them. Changes in

other constituents such as additives will have to be considered as will data obtained on patterns of smoking. If population studies enroll subjects who have switched to brands with varying smoke yields one or more times, the probability of detecting differences in FEV_1 or other parameters would be more difficult. Special efforts should focus on observations made of asymptomatic and symptomatic individuals with lung function abnormalities. It will probably be relatively easier to detect differences in the rate of pulmonary function deterioration between the regular and the lower "tar" and nicotine cigarette smokers in this group.

Priorities for Research Recommendations

The primary public health concern is the effect of the lower "tar" and nicotine cigarette on the individual's health. The second concern is the mechanism of the effect, and the third is the specific agent involved in stimulating the mechanism. The first need is to establish whether there is a measurable difference between smokers of regular and of lower "tar" and nicotine cigarettes. The epidemiologic approach to the problem may yield the greatest amount of valuable information in the most rapid manner, but population studies may not show differences in the development of chronic lung disease, since it is not known whether the etiologic component of smoke is altered in the currently marketed lower "tar" and nicotine cigarettes. Therefore, parallel research is necessary to a better understanding of the pathogenesis of COLD and identification of the responsible smoke component. A combination of epidemiologic studies designed to answer broad questions and human, animal, and *in vitro* studies will be required to define the entire problem. The epidemiologic studies will determine whether or not the lower "tar" and nicotine cigarettes have a health benefit or whether a potential benefit is negated either by changes in smoking patterns or by ignoring the agents responsible for inducing COLD. Topographic and dose-response information is required for the human studies. The final and perhaps most beneficial aspect of the research would be the elimination of the offending agents from cigarettes.

Investigation of the distal air spaces or lung parenchyma where the destructive component occurs in emphysema has received recent emphasis with new approaches and measurements. Therefore, investigation of this area may offer a greater possibility for significant new data. To date, studies of air flow characteristics, airway reactivity, and morphology have provided data concerning the chronology of the disease but have not pointed to the mechanism by which lung damage in emphysema is produced. Much of the benefit of basic research hinges on a better predictability of the topography of smoking and dose-response relationships. Information learned in the basic studies

can be translated into or used in epidemiologic studies, while the data obtained from epidemiologic studies can offer directions for the finer tuning of basic research. All of this would provide more information about the pathogenesis of chronic obstructive lung diseases and their potential alteration by lower "tar" and nicotine cigarettes.

The problem of passive exposure to cigarette smoke of different types of cigarettes also needs consideration. However, determination of the impact of lower "tar" and nicotine cigarette smoke on active smoke inhalation presents difficulties significant enough to render to low priority the passive smoking investigation at this time. Future dose-response data, especially determination of thresholds, would offer a lead into the area of passive smoking.

Research Recommendations

1. High priority should be given to a study of the distribution, partitioning, and penetration of regular and lower "tar" and nicotine smoke into the lung, including quantitation of and adjustment for any changes in the pattern of smoking by smokers of lower "tar" and nicotine cigarettes. Individuals in the specialized fields of aerosol physics, pharmacology, and toxicology should be involved in answering this question.
2. Parallel priority should be given to epidemiologic studies, preferably by adding to ongoing longitudinal and cross-sectional studies the data necessary to determine brand-related history. Higher and lower "tar" and nicotine cigarette smokers should be compared for differences in symptoms, morbidity, physiologic measurements, and mortality relating to COLD. Special attention should be given to people with identified disease or whose pulmonary function is deteriorating at an accelerated rate. New studies should be started if it is not possible to supplement the ongoing studies.

   Several ongoing epidemiological studies have been identified: (1) the Tucson Epidemiologic Study of Obstructive Lung Disease at the University of Arizona (Dr. Benjamin Burrows); (2) the Emphysema Screening Center Study of smokers and nonsmokers at the University of Oregon at Portland (Dr. Sonia Buist); (3) the Johns Hopkins University study of risk factors in chronic lung disease in Baltimore (Dr. Harold Menkes and colleagues); (4) the study of smokers in the Kaiser Permanente Health Care Plan (Dr. Diane Petitti); and (5) the Nurses Health Study at Harvard University (Dr. Frank Speizer). Statistical data to be collected by the National Center for Health Statistics, such as the Health and Nutrition Examination Survey, should be oriented to the collection of a detailed history of smoking, and followup studies should include spirometry. Data from the National Health Interview Survey and the National Death Index may also be useful.

3. The rapid clinical evaluation of the recently developed biochemical tests that measure products of lung elastin degradation and that can be detected in the plasma or urine should be carried out. If these prove both specific and sensitive, the time involved in carrying out the human epidemiologic research could be shortened.
4. Human, animal, and *in vitro* research that studies the mechanisms responsible for COLD and their possible alteration by lower "tar" and nicotine smoke should receive emphasis. Although the elastase-inhibitor imbalance hypothesis is well supported by experimental studies, confirmation of this mechanism is required for human disease. Verified animal models of emphysema induced by cigarette smoke exposure are not available at this time, but if such a model can be identified, it should be exploited. Investigation should involve airway factors, parenchymal alterations, and alterations in defense mechanisms that can be studied in short-term or subacute experiments. Biochemical, histological, and ultrastructural studies are required for correlation with exposure to smoke products or components from regular or lower "tar" and nicotine cigarettes. Dosimetry or exposure levels for these studies can be drawn from topographic and epidemiologic studies. Research on both animal and human tissue, cells, and lung lavage fluid is required.

Much progress has been made in recent years in the study of the mechanisms of lung damage relating to cigarette smoke. However, chronic bronchitis and emphysema are potentially devastating illnesses that have no curative treatment. Elimination of cigarette smoking would significantly reduce their public health importance. It is imperative that we define as soon as possible any differences in the effect of currently manufactured lower "tar" and nicotine cigarettes in the pathogenesis of these diseases.

Summary

1. The relationship between cigarette smoking and chronic obstructive lung disease (COLD) is well documented. The constituents of cigarette smoke that are responsible are currently not known. Whether a difference in risk of COLD has occurred with lower "tar" and nicotine cigarettes as compared with higher "tar" and nicotine cigarettes is currently unknown.
2. Cigarette smoking is associated with the release by alveolar macrophages of an increased amount of the elastolytic enzymes, which degrade alveolar tissue, and with reduced activity of alpha$_1$-antitrypsin, the primary elastase inhibitor. This mechanism has not yet been directly related to the development of human emphysema. To date there are no published studies that compare

the effects of higher versus lower "tar" and nicotine cigarettes on elastolytic enzymes and inhibitor activity.

3. Cigarette smoke also contains relatively high levels of oxides of nitrogen. The nitrogen oxides produce lung damage in animals that is similar to that induced in humans by cigarette smoke. The oxides of nitrogen may be responsible for the early lesions of human emphysema.
4. An individual's smoking pattern is one of the most important determinants of the relative concentration of smoke constituents that reach the lungs and of the subsequent response of the airways to smoke inhalation. Holding smoke in the mouth before inhaling it into the lungs produces less response of the airways than direct inhalation, which causes spirometric changes indicative of bronchoconstriction. This effect is independent of the "tar" content of the cigarette.
5. Pulmonary mucous hypersecretion and symptoms of cough and phlegm appear to be affected by the "tar" content of cigarette smoke. The development of airway obstruction is closely related to the number of cigarettes smoked. Smokers of lower "tar" and nicotine cigarettes who compensate by smoking more or inhaling more deeply might thereby increase their risk of developing obstructive airway disease.
6. Population studies that have examined the rate of decline of lung function in relation to the number of cigarettes smoked have shown variable results, and most of the available data do not relate lung function to cigarette yield. Overall, the mean difference between the rate of decline of FEV_1 in asymptomatic smokers and nonsmokers is very small, but there is a subgroup of the smoking population that shows more rapid decline and is apparently more likely to develop significant pulmonary disease.

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