CHAPTER 2

HEALTH EFFECTS OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE

CONTENTS

Introduction

In 1964, the first Report of the Surgeon General on smoking and health (US PHS 1964) determined that cigarette smoking was a cause of lung cancer in men and probably a cause of lung cancer in women. That Report also noted causal relationships between smoking and other cancers, as well as chronic lung disease. Subsequent Reports have described associations, both causal and noncausal, between tobacco smoking and a wide range of acute and chronic diseases. Epidemiological investigations have documented the effects of tobacco smoking in humans; complementary laboratory investigations have elucidated some of the mechanisms through which tobacco smoke causes disease.

More recently, the effects of the inhalation of environmental tobacco smoke by nonsmokers have become a pressing public health concern. Nonsmokers, as well as active smokers, inhale environmental tobacco smoke, the mixture of sidestream smoke and exhaled mainstream smoke. Various terms have been applied to the inhalation of environmental tobacco smoke by nonsmokers; the terms "involuntary smoking" and "passive smoking" are the most prevalent and are often used interchangeably by researchers and the public.

Many of the known toxic and carcinogenic agents found in mainstream cigarette smoke have also been demonstrated to be present in sidestream smoke. Furthermore, the combustion conditions under which sidestream smoke is produced result in the generation of larger amounts of many of these toxic and carcinogenic agents per gram of tobacco burned than the conditions under which mainstream smoke is generated (see Chapter 3). The characteristics of environmental tobacco smoke also differ from those of mainstream smoke because the sidestream smoke ages before it is inhaled and the mainstream smoke exhaled by the active smoker is modified during its residence in the lung. There is no evidence to suggest that environmental tobacco smoke has a qualitatively lower toxicity or carcinogenicity than mainstream smoke per milligram of smoke inhaled. In fact, the available evidence suggests that sidestream smoke contains higher concentrations of many known toxic and carcinogenic agents per milligram of smoke and is more tumorgenic than mainstream smoke in animal testing (Wynder and Hoffmann 1967). As a result, involuntary smoking should not be viewed as a qualitatively different exposure from active smoking, but rather as a low-dose exposure to a known hazardous agent--cigarette smoke.

Evaluation of Low-Dose Tobacco Smoke Exposures

Assessment of the health effects of any environmental exposure poses methodological problems, particularly when exposure levels

are low and therefore the magnitude of the expected effect is small. The evaluation of an effect due to a low-dose exposure such as environmental tobacco smoke requires the investigation of populations with differences in exposure large enough so that an effect could be anticipated. The population studied must also be of sufficient size to quantitate the effects in the range of interest with precision. Failure to fulfill these requirements may produce a false-negative result in a study of a low-dose exposure.

Exposure to environmental tobacco smoke is a nearly universal experience in the more developed countries, so the identification of a truly unexposed population is very difficult. Epidemiological studies of involuntary smoking have attempted to identify populations with lower exposure and higher exposure to environmental tobacco smoke, most notably by examining nonsmokers exposed to tobacco smoke generated by the smokers of their family. The effects of environmental tobacco smoke have been investigated in a number of populations throughout the world. The diversity of these populations is likely to be accompanied by a similar diversity of their exposure to environmental tobacco smoke. Thus, the gradient in exposure to environmental tobacco smoke between the "exposed" and "nonexposed" groups is likely to vary widely among the reported studies. For example, the husband's smoking status may be a strong predictor of total exposure to ETS in traditional societies, such as Japan and Greece, where the wife's exposure outside the home is limited. In contrast, the husband's smoking status in the United States, where substantial exposure may occur outside the home, may not be as predictive.

Sample size considerations are of particular concern for the epidemiological studies of lung cancer and involuntary smoking. Because the frequency of lung cancer in nonsmokers is low, many of these studies often included small numbers of nonsmokers and lacked the statistical power necessary to find the modest effect expected from this low-dose exposure. Given the constraints of sample size and the varying gradients of exposure, it would be expected that some studies would find no association between involuntary smoking and lung cancer, and that other studies would find associations that lacked statistical significance. Nonuniformity of the data, however, does not imply a lack of effect; rather, it is the coherence and trends of the evidence that must be judged. Thus, this Report examines the entire body of evidence on the health effects of involuntary smoking, as the basis for its conclusions.

In evaluating the hazards posed by an air pollutant such as environmental tobacco smoke, laboratory, toxicological, human exposure, and epidemiological investigations provide relevant data. Each approach has limitations, but the insights each provides are complementary. Epidemiological investigations describe the effects

in human populations, but their results must be interpreted in the context of the other types of investigations.

Risk assessment techniques have also been used to characterize the potential adverse health effects of human exposures to environmental pollutants, particularly those at low levels. The four steps of risk assessment have been described by the National Academy of Sciences as hazard identification, dose-response assessment, exposure assessment, and risk characterization (NAS 1983). Risk assessment has also been used to describe the consequences of exposure to ETS. However, unlike many environmental exposures for which risk assessment represents the only approach for estimating human risk, the health effects of ETS exposure can be examined directly using epidemiological methods. Although this Report reviews several risk assessments done by individual researchers on ETS, its conclusions are based on the laboratory, toxicological, and epidemiological evidence.

Extrapolation of Active Smoking Data to Environmental Tobacco Smoke Exposure

Comparison of Mainstream Smoke and Sidestream Smoke

A detailed comparison of mainstream and sidestream smoke can be found in Chapter 3. Mainstream smoke (MS) is the term applied to the complex mixture that is inhaled by the smoker from the mouthpiece of a cigarette, cigar, or pipe with each puff. Sidestream smoke (SS) is the aerosol that comes from the burning end of the cigarette, pipe, or cigar between puffs. Environmental tobacco smoke (ETS) is the term applied to the combination of SS and exhaled MS, which is diluted and aged in an area where smoking has taken place. Most of the existing data on mainstream and sidestream smoke characteristics relate to cigarette smoking and relatively little information is available pertaining to cigar and pipe smoking.

Because both MS and SS are generated from the tip of the burning tobacco product, it is not surprising that their compositions are similar. Of the thousands of compounds identified in tobacco smoke, many have been identified as present in both MS and SS. Among these are carcinogens, gases such as carbon monoxide and the oxides of nitrogen, and nicotine. Since there is a wealth of information relating to the toxicity and carcinogenicity of MS, it should be emphasized again that ETS cannot be treated as a new environmental agent for the purpose of assessing health risks. The presence of the same agents in MS and SS leads to the conclusion that ETS has a toxic and carcinogenic potential that would not be expected to be qualitatively different from that of MS. Quantitative differences between the active smoker's exposure to MS and the involuntary smoker's exposure to ETS are likely to be the more important

determinant of the differing magnitudes of risks associated with these two exposures.

Differences in the composition of MS and SS primarily reflect their generation at different temperatures in different oxygen environments. Also, SS is diluted very rapidly, under most circumstances, and has the opportunity to age before inhalation. The involuntary smoker usually inhales ETS, not SS, the aerosol that comes from the tip of a burning cigarette. In considering the characteristics of SS, it must be emphasized that much of the existing data about the composition of MS and SS is derived from studies carried out in special chambers rather than by sampling MS and SS generated by smokers. In these chamber studies, SS has been sampled by a probe located close to the burning tip. This experimental situation clearly differs from that of a room with one or more smokers freely smoking. In that situation, SS is mixed with exhaled MS, diluted and aged. Nevertheless, these chamber studies provide very useful information about the compounds present in the SS. These studies have established that SS in comparison with MS has a higher pH, smaller particle size, and more carbon monoxide, benzene, toluene, acrolein, acetone, pyridine, ammonia, methylamine, nicotine, aniline, cadmium, radon daughters, benzo[a]pyrene and benz[a]anthracene.

Comparison of the relative concentrations of the various components of SS and MS smoke provides limited insights concerning the toxicological potential of ETS in comparison with active smoking. As described above, SS characteristics, as measured in a chamber, do not represent those of ETS, as inhaled by the nonsmoker under nonexperimental conditions. Further, the dose-response relationships between specific tobacco smoke components and specific diseases are not sufficiently established for the necessary extrapolations from active smoking to environmental tobacco smoke exposure for individual agents. For that reason the extrapolations in this section are confined to the dose-response relationships of whole smoke for those diseases with established dose-response relationships.

With regard to the potential of ETS to cause lung cancer, undiluted SS has 20 to 100 times greater concentrations of highly carcinogenic volatile N-nitrosamines than MS (Brunnemann et al. 1978) as well as higher concentrations of benzopyrenes and benz[a]anthracenes.

For nonmalignant effects on airways and the lung parenchyma, the agents responsible for the development of acute and chronic respiratory disease have not been identified, although many tobacco smoke components have been shown to cause lung injury (US DHHS 1984). Presumably, both vapor phase (gaseous) and particulate phase (solid) components of MS are involved. Both airways disease and

parenchymal disease are probably a response to the total burden of respiratory insults, some of which, like active smoking, may be sufficient by themselves to cause physiologic impairment and ultimately, clinical disease. Others, such as ETS, may contribute to the total burden but be insufficient, individually, to cause clinical disease.

Deposition of Mainstream Smoke and Sidestream Smoke and Environmental Tobacco Smoke Dose Estimates

The dose of tobacco smoke delivered to the airways and alveoli depends, among other factors, on the volume of MS, SS, or ETS inhaled, on the rate and depth of inhalation, and on the size, shape, and density of the individual particles or droplets. Patterns of deposition of MS in the lungs have been described, but similar information about deposition patterns for ETS is not yet available. Without such data, it is necessary to extrapolate from the information on MS.

The major factors that affect the pattern of deposition and retention for particles are particle size distribution and breathing pattern. The particle size range and mean aerodynamic diameter for particulates in sidestream smoke are similar to those of mainstream smoke (particle size range of 0.01 to 0.8 μm for sidestream smoke and 0.1 to 1.0 μm for mainstream smoke, and mean aerodynamic diameter 0.32 μm for sidestream smoke and 0.4 μm for mainstream smoke) (see Chapters 3 and 4). The deposition site is determined largely by the size of the particles, with large particles being deposited preferentially in the nasopharynx and large conducting airways. Smaller particles are deposited more peripherally, and very small particles tend to be exhaled and to have a very low deposition fraction. The particulates of ETS, because of their size range, are likely to be deposited peripherally.

The breathing patterns for the inhalation of MS and ETS are also different; MS is inhaled intermittently by the smoker with an intense inhalation, often followed by a breathhold that results in a more equal distribution. Environmental tobacco smoke, on the other hand, is inhaled continuously with tidal breaths when the passive smoker is at rest and with deeper inhalations when the passive smoker is physically active. Breathholding does not normally occur with tidal breathing.

Estimates of the equivalent exposure, in terms of cigarettes per day, resulting from ETS, as compared with MS, vary quite widely and depend on the way in which the estimates were made. Repace and Lowrey (1985) estimated that nonsmokers in the United States are exposed to from 0 to 14 mg of tobacco tar (average 1.4 mg) per day. Vutuc (1984) estimated that the exposure to environmental cigarette smoke is equivalent to 0.1 to 1 cigarette per day actively

smoked. Estimates of ETS exposure, based on cotinine measure ments, suggest that involuntary smokers absorb about 0.5 to 1 percent of the nicotine that active smokers absorb (Jarvis et al. 1984; Haley and Hoffmann 1985; Wald et al. 1984; Russell et al. 1936).

Dose-Response Relationships and Threshold for Risk

Dose-response relationships for active smoking can provide insights into the expected magnitude of disease resulting from the exposure of nonsmokers to ETS. These data are reviewed to determine whether disease can be expected in association with ETS.

Data from cohort and case-control studies demonstrate dose-response relationships for lung cancer, which extend to the lowest levels of reported active smoking. The dose-response relationship of active smoking with lung cancer risk has been described by several investigators in several different data sets (Whittemore and Altshuler 1976; Doll and Peto 1978; Pathak et al. 1936). Although the mathematical forms of these models vary, none have included a threshold level of active smoking that must be passed for lung cancer to develop.

The dose-response relationship for active smoking and lung cancer has been used to project the lung cancer risk for nonsmokers (Vutuc 1984). Such projections yield risk estimates of 1.03 to 1.36 for exposures, considered to be reasonable estimates of involuntary smoking exposures, i.e., 0.1 to 1.0 cigarettes per day. The reference population for these risk estimates is the risk for nonsmokers as a group, including those with higher and those with lower exposures to environmental tobacco smoke. In contrast, the reference population for the risk estimates in studies of involuntary smoking is the lung cancer risk in only that group of nonsmokers who have lower exposure to ETS. Comparisons of lung cancer risk estimates from active smoking studies with those from involuntary smoking studies require reference to the same exposure group for proper interpretation. In general, the lung cancer experience of all nonsmokers (i.e., those with higher and lower involuntary smoking exposure combined) has been used to establish the reference rate of lung cancer occurrence (i.e., set as a risk of 1) in studies of active smoking. The use of all nonsmokers as the reference group averages the lower risks of nonsmokers with less ETS exposure with the higher risks of those with more ETS exposure. Thus, with the relative risk for the entire group of nonsmokers set to unity, the relative risk for nonsmokers with lower exposure is below 1 and that for the group with higher exposure is above 1. As a consequence, relative risk estimates from studies of involuntary exposure cannot be directly compared with risk estimates extrapolated from active smoking, unless comparison to a single level of exposure is possible. Failure to

consider the differences between the reference populations explains the apparent discrepancy noted by Vutuc.

Consider, for example, the mortality study reported by Hirayama (1981a). In this study, the relative risk of lung cancer for nonsmoking wives of smoking husbands (current and former) compared with nonsmoking wives of nonsmoking husbands (as calculated from Figure 1 in Hirayama 1981a) was 1.78. If the relative risk for nonsmoking wives of nonsmoking husbands were expressed in relation to the combined group of nonsmoking women, then a value of 0.63 is obtained, while with a similar calculation, that for nonsmoking wives of smoking husbands (both current and former), yields a value of 1.12. Thus, when the appropriate comparison is made, the risk estimates developed by extrapolation of the active smoking data (1.03 to 1.36) closely approximate those actually found in a study of lung cancer risk due to involuntary smoking.

Dose-response relationships between active smoking and the level of lung function, the rate of decline of lung function in adult life, and the development of chronic airflow obstruction are well established (US DHHS 1984). Different measures of dose have provided the strongest correlation with functional decline in different studies. Pack-years, a cumulative dose measure, was the strongest predictor of the level of forced expiratory volume in 1 second (FEV_1) in the Tucson epidemiologic study (Burrows, Knudson, Cline et al. 1977). Duration of smoking and the amount smoked were found to be the best predictors in male subjects in a study of three U.S. communities (Beck et al. 1981), and pack-years was the best predictor in female subjects. In both of these studies, however, the estimated dose accounted for only about 15 percent of the variation of age- and height-adjusted FEV_1 levels. The relatively low predictive capability of cigarette smoking variables in these studies most likely reflects a lack of information on the determinants of individual susceptibility to tobacco smoke. Further, exposure variables obtained by questionnaire, such as the number of cigarettes smoked daily, may only roughly approximate the dose delivered to target sites in the respiratory tract. Many factors, such as puff volume, lung volume at which inhalation starts, and airways geometry will influence the smoke dose and its distribution within the lungs. Extrapolation from the results of these studies to the pulmonary effects of exposure to ETS is, therefore, likely to be inaccurate.

Another approach for assessing low-dose exposures is to consider the information available from studies involving children and teenagers who have recently taken up smoking. Even with brief smoking experience, cross-sectional studies of active cigarette smoking by children and adolescents have demonstrated an increased frequency of respiratory symptoms (Rawbone et al. 1978; Rush 1974; Bewley et al. 1973; Seely et al. 1971) and small but statistically

significant reductions in lung function (Seely et al. 1971; Peters and Ferris 1967; Lim 1973; Walter et al. 1974; Backhouse 1975; Woolcock et al. 1984). Longitudinal studies involving children and adolescents have demonstrated that a physiologic impairment attributable to smoking may be found in some children by age 14 and may be present after only 1 year of smoking 10 or more cigarettes per week in children with previously normal airways (Woolcock et al. 1984), and that relatively small amounts of cigarette use may lead to significant effects on FEV_1 and on the growth of lung function in adolescents (Figure 1) (Tager et al. 1985).

When considering the risk of low-dose exposures for the development of chronic respiratory disease, the existence of a spectrum of risk and a distribution of dose within the population should be taken into consideration. The characteristics of the part of the population most susceptible to involuntary smoke exposure is still being clarified. Evidence is accumulating that airways hyperresponsiveness, atopy, childhood respiratory illness, and occupational exposures may all influence response to ETS. Current understanding of lung injury suggests that individuals with one or more of these characteristics that place them at the most sensitive end of the susceptibility curve may be the most likely to develop symptoms or functional changes as a result of ETS exposure. Dose of ETS also varies in the population, and the coincidence of high dose and increased susceptibility may convey a particularly high risk. Furthermore, ETS exposure may damage lungs that are also affected by other insults.

Pathophysiologic Considerations

Cancer

Carcinogenesis refers to the process by which a normal cell is transformed into a malignant cell with uncontrolled replication. Carcinogenesis has been conceptualized as a multistage process involving a sequence of alterations in cellular DNA that terminate with the development of a malignant cell. Agents acting early in this sequence are referred to as initiators; those acting later are referred to as promoters. Compounds with both initiating activity and promoting activity have been identified in tobacco smoke.

Carcinogenesis reflects DNA damage; although some repair may take place, biological models have not suggested that there is a threshold of damage that must be exceeded. Rather, carcinogenesis has been considered to involve a series of changes, each occurring at a rate dependent on the dose of a damaging agent. Higher doses increase the probability that the entire sequence will be completed, but lower doses may also lead to malignancy.

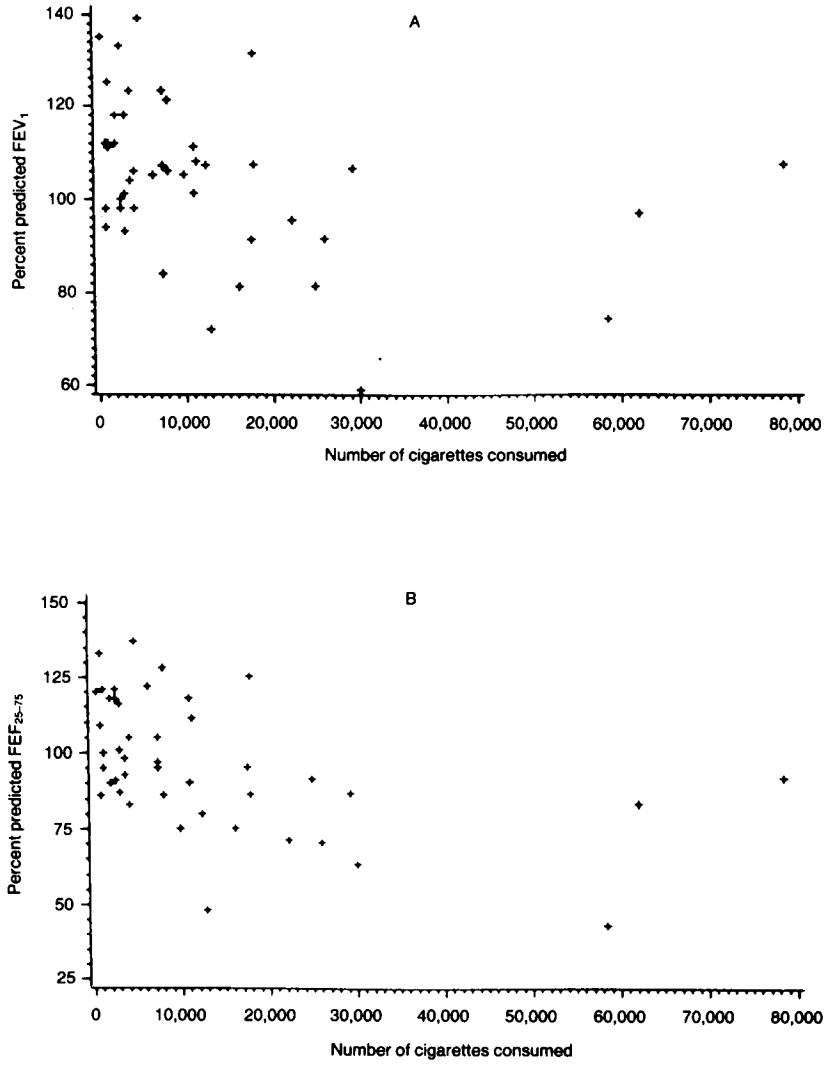

FIGURE 1.—Relationship between levels of predicted for FEV_1 (A) and FEF_{27-75} (B) at examination 8 and cumulative number of cigarettes smoked during examinations 4 through 8

NOTE: Men and women combined (N = 44).
SOURCE: Tager et al. (1985).

Lung Disease

The noncarcinogenic pathophysiologic effects of active smoking on the respiratory tract can be separated into (1) effects on the airways and (2) effects on the lung parenchyma. In the airways, the structural changes include inflammation in the small airways and mucous gland hypertrophy and hyperplasia. In the parenchyma, the main structural change is alveolar wall destruction. Both the airways and the parenchymal changes are caused by active smoking, but the interrelationships of these changes are not clear. They may be independent pathophysiologic processes, linked only by their joint association with tobacco smoking.

As discussed earlier, there is evidence showing an approximately linear dose-response relationship between FEV_1 level and amount smoked; however, the dose-response relationships have not been as well described for the underlying pathophysiologic changes in the airways or in the lung parenchyma. Host factors and other environmental factors presumably interact with active smoking to affect an individual's risk for the development of disease. In this regard, present evidence would suggest that only 10 to 15 percent of smokers develop clinically significant airflow obstruction, although parenchymal and airways changes can be demonstrated in a substantially higher percentage at autopsy (US DHHS 1984).

Extrapolation from the evidence on active smoking to the likely effect of exposure to environmental tobacco smoke on the airways and parenchyma suggests that pathophysiologic effects on both the airways and the lung parenchyma might be expected. Because the dose of smoke components from ETS exposure is small in comparison with the dose from active smoking, the extent of lung injury would most likely also be much smaller than that found in active smokers. Small changes in the lung may be below the threshold for detection on pulmonary function testing. If clinically significant chronic airflow obstruction occurs in nonsmokers exposed to ETS, the risk is likely to be concentrated among those individuals highly susceptible to the airway or parenchymal effects of cigarette smoke. This susceptible group may include individuals with bronchial hyperresponsiveness and with other, as yet unidentified, genetic and familial risk factors. Identifying the risk factors for susceptibility to the airway and parenchymal effects of both mainstream smoke and ETS is an important priority. The dose of environmental tobacco smoke received by the nonsmoker is unlikely, by itself, to be sufficient to cause a clinically significant degree of *parenchymal* disease (emphysema) unless an individual is at the extreme end of the susceptibility distribution. Any particulate load is likely to increase the elastase burden in the lungs by causing an influx of neutrophils. However, only in the individual with very inadequate lung defenses, specifically severe deficiency of protease inhibitor (Pi) associated

with the PiZZ or other phenotypes, are modest particulate exposures likely to increase the risk for disease to an appreciable extent.

The development of acute and chronic *airway* disease or symptoms of cough, phlegm production, and wheeze may require a considerably smaller exposure than changes in the lung parenchyma, and it is not unreasonable to hypothesize that these symptoms may be related to repeated and continuous exposure to ETS in the susceptible individual. Strong evidence that low-dose active smoking causes increased rates of respiratory symptoms and functional impairment comes from the studies of children and adolescents discussed earlier (Woolcock et al. 1984; Tager et al. 1985). Because of the length of exposure, it is likely that these reflect airway rather than parenchymal effects.

Another pathophysiological mechanism by which exposure to ETS may increase an individual's risk for the development of chronic airflow obstruction is through respiratory viral infections. Mounting evidence indicates that the very young child (under 2 years of age) exposed to ETS is at increased risk for lower respiratory tract viral infections (Harlap and Davies 1974; Colley 1974; Colley et al. 1974; Leeder et al. 1976a; Fergusson et al. 1981; Dutau et al. 1979; Pedreira et al. 1985). There is also increasing, though still inconclusive, epidemiologic evidence that respiratory viral infections in early life may be associated with an accelerated decline in FEV_1 and, therefore, an increased risk for the development of chronic airflow obstruction in adult life in smokers (Burrows, Knudson, Lebowitz 1977; Samet et al. 1983). By increasing the occurrence of viral infections of the lower respiratory tract in early life, exposure to ETS in childhood may have an appreciable, but indirect, effect on the risk for the development of chronic airflow obstruction in adult life. The structural basis for this increased susceptibility has not yet been elucidated, however. Furthermore, the child whose parents smoke is also more likely to take up smoking than is the child of nonsmoking parents. Thus, the child made susceptible to the effects of active smoking by prior ETS exposure is also more likely to become an active smoker.

The possibility that exposure to constituents of tobacco smoke in utero may exert a prenatal effect must also be considered. This exposure is clearly not the same as ETS exposure, since the lungs of the fetus are not being exposed to ETS; rather, the developing fetal lung is exposed to compounds absorbed by the mother and delivered to the fetus transplacentally. Evidence of an in utero effect in pregnant rats has been reported by Collins and coworkers (1985). These investigators reported that pregnant rata exposed to smoke from day 5 to day 20 of gestation, in comparison with control rats, showed reduced lung volume at term and saccules that were reduced in number and increased in size as a result of the reduced formation

of saccule partitions. These hypoplastic lungs showed an internal surface area that was decreased. Whether this study in rata has any relevance to humans is not yet clear, but this issue deserves further investigation.

Whether continued exposure to ETS during childhood, while the lung is remodeling and growing, affects the process of growth and remodeling is not yet clear. In general, rapidly dividing cells and immature organs are more susceptible to the effects of environmental toxins than are cells undergoing a normal rate of division and mature organs. Apart from the evidence, cited above, linking lower respiratory tract viral infections in very early life to an accelerated decline of FEV_1 in adult life, there is no information yet to link the rate of growth of lung function during childhood to the rate of decline of lung function in adult life because the necessary longitudinal studies have not been done. More information is needed to describe the relationship of exposure to ETS at various times during childhood to the maximal level of lung function achieved at full lung growth.

Methodological Considerations in Epidemiologic Studies

Measurement of Exposure

In assessing the health effects of ETS exposure, as with other environmental pollutants, accurate assessment of exposure is critical for obtaining estimates of this agent's effects. Both random and systematic misclassification of the exposures of subjects in an investigation are of concern. Random misclassification refers to errors that occur at random; the consequence of such random misclassification is to bias toward finding no effect. Systematic misclassification refers to nonrandom errors in exposure assessment; the consequence may be to bias toward a greater or lesser effect than is actually present. Biased answers in response to a questionnaire may introduce systematic misclassification.

Some misclassification occurs in most observational (nonexperimental) epidemiological studies, and is inherent in all epidemiological studies of ETS. Tobacco smoking is ubiquitous in nearly all environments; few people escape being exposed to ETS. Thus, the exposure variables for ETS in epidemiological studies do not separate nonexposed subjects from exposed subjects; rather, they identify groups with more or less exposure, or with a qualitative or semiquantitative gradient of exposure.

In assessing exposure to ETS, the information should cover the biologically appropriate time period for the health effect of interest and be collected in a form that permits the construction of biologically appropriate exposure measures. However, the collection of a full lifetime history of ETS exposure, as in a study of malignancy, may not be feasible, and the accuracy of the informa-

tion may be limited. In evaluating the effects of ETS exposure, cumulative exposure, duration of exposure, and intensity of exposure may each influence the magnitude of effects, as may the timing of exposure in relation to age and level of development.

Because of the difficulties inherent in assessing exposures through questionnaires, increased emphasis has been placed on measuring exposure through the use of molecular or biochemical markers. With available markers, this approach is limited to providing an indication of recent (within 48 hours) exposure, which may not necessarily correlate with past exposure. A marker has not yet been devised for total integrated dose. Nevertheless, biological markers provide another method for classification of current exposure, and a standard for validating questionnaires.

The strengths and weaknesses of the existing methods of measuring exposure are further discussed below.

Atmospheric Markers

A number of different markers of atmospheric contamination by tobacco combustion products can be feasibly measured. Ideally, the atmospheric levels of the air contaminant or class of contaminants that are implicated in producing the adverse health effects would be measured. A variety of contaminants have been measured as indicators of ETS, but no single measure can adequately index all of its myriad components. Further, some contaminants are produced by sources of environmental contamination other than tobacco smoke. Nicotine is absorbed only from tobacco and tobacco combustion products.

Some of the pollutants that have been measured include (1) carbon monoxide, (2) respirable suspended particulates (RSP), (3) nicotine, (4) a number of aromatic hydrocarbons, such as benzene, toluene, benzo-pyrene, and phenols, and (5) acrolein. Some of these are in the vapor phase and some in the particulate phase. Some, such as nicotine, may exist in one phase (particulate) in MS and in the other (gas) phase in SS. Until more is learned about the contaminants and their physical state in ETS, the results of monitoring for a particular ETS component will be difficult to relate to its disease-causing potential. At a practical level, the technology for measuring nicotine levels and RSP levels is available and accurate.

Personal Monitoring

Both active and passive personal monitors can be used to measure an individual's total exposure to an air contaminant at the breathing zone. Active personal monitoring systems employ pumps to concentrate the air contaminants on a collection medium for laboratory analysis or to deliver the air to a continuous monitor. Passive

personal monitoring systems use diffusion and permeation to concentrate gases on a collection medium for laboratory analysis. Personal monitoring should provide a more accurate estimate of the dose of a contaminant than area monitoring, because the actual air in the breathing zone is sampled and the subject's time-activity pattern is inherently considered.

As with area monitoring, the results for a particular component of ETS may not adequately characterize exposure to other components responsible for a particular disease or effect. Respirable suspended particulates can be measured with accuracy and give a reasonably accurate measurement of current exposure.

Questionnaires

The questionnaire has been the most frequently used means of estimating exposures for epidemiological investigations. Questionnaires typically have obtained information about the smoking habits of parents, spouses, or other family members and often about exposure outside the home. From this information, the subject is classified as exposed or not exposed to ETS, and the extent of exposure may be estimated.

The questionnaire approach for exposure estimation has several potential limitations. First, the information obtained cannot exhaustively cover lifetime exposure to ETS; therefore, a completely accurate reconstruction of integrated dose over the years cannot be achieved. Second, in evaluating ETS exposure in the home, the usual daily smoking of the smokers has often been used as a measure of exposure intensity at home. This assumption may not be correct, since smoking does not occur only in the home. For example, a one-pack-a-day smoker may smoke only five cigarettes a day in the home environment and smoke the rest at work or elsewhere outside the home. Third, quantitation of exposure in the workplace is inherently difficult because of changes in jobs and the varying exposure in any particular workplace.

Despite these shortcomings, the information obtained by questionnaires does discriminate between more exposed and less exposed subjects. The evidence validating the questionnaire method is strongest for domestic exposure. In several studies, levels of cotinine in body fluids have varied with reported exposure to tobacco smoke at home (Greenberg et al. 1984; Wald and Ritchie 1984; Matsukura et al. 1984; Jarvis et al. 1984). In fact, residence with a smoker may identify a population that is more tolerant of ETS, and therefore more likely to be exposed outside the home. Evidence in support of this speculation is provided by a study of urinary cotinine levels in nonsmoking men in the United Kingdom (Wald and Ritchie 1984). In this study, the men married to women who smoked reported a

greater duration of exposure outside the home than men married to women who did not smoke.

Until accurate and inexpensive exposure markers are available for cumulative ETS exposure, the questionnaire approach will remain the simplest means of obtaining exposure information. It is, therefore, important to consider the misclassification that can be introduced by using this indirect measure of exposure. In studies of the effect of ETS exposure, two types of misclassification are of concern: misclassification of current or former smokers as never smokers and misclassification of the extent of ETS exposure.

Because active smoking has a greater effect on the lungs than exposure to ETS, the inclusion of active smokers within a larger group of nonsmokers may lead to the finding of a significant effect on lung function, which is actually attributable to active smoking rather than to involuntary smoking. Misclassification of undeclared active smoking is a particularly important source of error in studies involving teenagers. Misclassification of smoking status is also of concern in case-control studies of the association between exposure to ETS and lung cancer. Information about smoking habits for these studies often comes from interviews with a surviving spouse or surrogate, who may have been a close family member, neighbor, or friend, or from a review of medical records. The smoking habits of the subject may be incorrectly reported. Classification of individuals who are current or former smokers as never smokers would lead to a spurious increase in the relative risk for lung cancer in nonsmokers exposed to ETS, because the smoking habits of spouses tend to be correlated. The extent of this bias in the case-control studies is uncertain. The proportion of people reported as never smokers, but who in fact did smoke in the past, is unknown. The proportion of current smokers who report themselves as nonsmokers can be estimated from studies using markers to validate questionnaires. Using biochemical markers of tobacco smoke absorption, the proportion would appear to be about 0.5 to 3 percent, depending on the population studied and the questionnaire used (Wald et al. 1981; Saloojee et al. 1982).

Misclassification of the extent of ETS exposure can also occur, and may reduce the observed risk if a nonsmoking spouse of a smoker is not exposed to smoke at home. Friedman and colleagues (1983), reporting on a survey of 38,000 subjects, noted that 47 percent of nonsmoking women married to smokers reported that they were not exposed to tobacco smoke at home.

Measurements of Absorption

The difficulties inherent in estimating exposure and dose have provided the impetus for the development of biological markers for exposure to both MS and ETS. The marker that at present holds the

highest promise is cotinine, the major metabolite of nicotine. Cotinine may be measured in saliva, blood, or urine. Numerous studies have demonstrated that there is good correlation between these measures of cotinine and the estimated exposure to tobacco smoke under laboratory conditions (Russell and Feyerabend 1975; Hoffmann et al. 1984) and under conditions of daily life (Russell and Feyerabend 1975; Feyerabend et al. 1982; Foliart et al. 1983; Wald et al. 1984; Wald and Ritchie 1984; Jarvis et al. 1984; Matsukura et al. 1984, Greenberg et al. 1984). Cotinine is probably the best marker for tobacco smoke intake because it is highly sensitive and specific for tobacco smoke and because it can be detected both in active smokers and in individuals exposed to ETS. Further details about cotinine and other markers are to be found in Chapter 4.

Potentially Confounding Variables

In any epidemiological study, the confounding factors must be considered and their effects controlled. Confounding refers to the biasing effect of a factor that independently influences the risk for the disease of concern and is also associated with the exposure under evaluation. Confounding is of particular concern when the effects of the exposure of interest are expected to be small.

The potential confounding variables depend on the health outcome of interest. For lung cancer, occupational exposures, diet, and exposure to other combustion products are of concern. For acute and chronic pulmonary effects, potential confounders include airways hyperresponsiveness, other indoor air pollutants, outdoor air pollution, respiratory tract infections, occupational exposure, and socioeconomic status, which may potentially influence disease risk through its environmental correlates. While this list is extensive, it may not be inclusive; in any single investigation it may not be possible to measure and control all potentially confounding variables.

Statistical Issues

In general, the evidence on active smoking in combination with the dosimetry of involuntary smoking leads to the conclusion that the effects of ETS on a population will be substantially less than the effects of active smoking. The effects of ETS on infants and young children are an important exception.

The association of ETS with an adverse effect in an individual study may reflect bias, chance, or a causal relationship. Statistical significance testing is used to quantitate the role of chance; by convention, a p (probability) value less than 0.05 is deemed statistically significant. A p value less than 0.05 means that the observed results would occur by chance less than 5 times out of 100, if there is

truly no association between ETS and the effect. The choice of 0.05 is arbitrary, and as the significance level declines, the probability that the observation could have occurred by chance lessens.

For effects of small magnitude, as may be anticipated for some consequences of exposure to ETS, a large study population may be necessary to demonstrate statistical significance. The absence of statistical significance for an association may reflect an inadequate sample size and is not always indicative of the absence of an association. In this regard, reports describing the absence of effects of ETS should provide the calculations needed to demonstrate the study's statistical power (ability to detect effects of the magnitude expected) or a confidence interval for the estimate of effect.

An additional statistical issue is the directionality of statistical significance testing. Either one-sided or two-sided tests may be used; in the first, only effects in one direction are considered a possibility, whereas two-sided tests consider the possibility of effects in opposing directions, i.e., increase or decrease of risk. Given the strength of the evidence on active smoking and disease risk, one-sided testing in the direction of an adverse effect seems appropriate for most potential consequences of ETS. However, one-sided tests have not been performed in all investigations of ETS; the use of two-sided tests makes these studies conservative, as statistical significance will less often be attained.

Respiratory System Effects of Involuntary Cigarette Smoke Exposure

This section reviews the evidence on involuntary smoking and the adverse physiologic effects, respiratory symptoms, and respiratory diseases in nonsmoking adults and children. Health effects related to fetal exposure in utero from active smoking by the mother are not discussed. Lung growth and development may be influenced by in utero exposure, and the effects of such exposures have not been separated from those of exposure after birth. More complete treatments of this issue have been published (US DHEW 1979; US DHHS 1980; Abel 1980; Weinberger and Weiss 1981).

This section begins with a review of the data on infants and children who are exposed primarily through parental smoking. The health effects examined are increased respiratory illnesses, of both the upper and the lower respiratory tracts, increased chronic respiratory symptoms and illnesses, and alterations in lung growth and development. Studies of adults, whose exposures to environmental tobacco smoke occur in a variety of settings, are examined with regard to symptoms and changes in measures of lung function. The potential for ETS to produce bronchoconstriction in asthmatic and nonasthmatic subjects is also examined.

Infants and Children

Acute Respiratory Illness

Longitudinal Studies

A number of studies, based on a variety of different designs, have examined the effects of involuntary smoking on the acute respiratory illness experience of children (Table 1). Several different end points have been evaluated in these investigations: hospitalization for bronchitis or pneumonia as assessed by hospital records (Harlap and Davies 1974; Rantakallio 1978); questionnaire assessment of hospitalization for bronchitis or pneumonia or of doctor's visits (Colley 1971; Leeder et al. 1976a) or both (Fergusson et al. 1981; Fergusson and Horwood 1985); questionnaire assessment of respiratory illness within the last year (Cameron et al. 1969; Schenker et al. 1983; Ware et al. 1984); chest illness before age 2 (Schenker et al. 1983); hospitalization for respiratory syncytial virus (RSV) infection (Sims et al. 1978; Pullan and Hey 1982); physician-diagnosed bronchitis, tracheitis, or laryngitis (Pedreira et al. 1985); and tonsillectomy as an indication of recurrent respiratory infection (Said et al. 1978). These diverse end points range from illnesses associated with a specific etiologic agent, e.g., RSV bronchiolitis, to clinician-diagnosed syndromes, e.g., bronchitis of undetermined etiology.

The possibility of reporting bias must be considered for the studies that have used questionnaires to measure illness experience. In most of these studies, parents, usually the mother, have responded for the child and reported on the child's illness experience. Some investigators have suggested that mothers with respiratory symptoms are more likely to report symptoms for their children and that stratification of subjects by the symptom status of their parents removes this element of recall bias (Lebowitz and Burrows 1976). Removal of symptomatic parents, however, may result in overcorrection for recall bias because cigarette smoking is associated with symptoms in the adult. This analytical strategy would not be expected to adjust for biased parental recall of early life events. Additionally, in all studies in which potential reporting bias was examined, control for parents' status reduced, but did not eliminate, associations of involuntary smoking with health outcomes (Colley et al. 1974, Leeder et al. 1976a,b; Schenker et al. 1983; Ware et al. 1984). Further, the consistency of these studies, in spite of differing study populations and methods, weighs against bias as the sole explanation for the effect of involuntary smoke exposure.

Harlap and Davies (1974) studied 10,672 births in Israel between 1965 and 1968 and observed that infants, whose mothers, at a prenatal visit, reported that they smoked, had a 27.5 percent greater hospital admission rate for pneumonia and bronchitis than children

TABLE 1.--Early childhood respiratory illness and involuntary cigarette smoking

Study	Subjects	Findings	Illness rates per 100				Comments
			By cigarette per day				
			0	1-10	11-20	20+	
Harlap and Davies (1974)	10,672 births, 1965-1968, Israel	Hospitalized, bronchitis pneumonia, first year of life RR=1.38	9.5	10.8	16.2	31.7	Prenatal smoking history; maternal smoking only Longitudinal study
Colley[1] (1971)	2,205 births, 1963-1965, England	Questionnaire, bronchitis/ pneumonia first year of life RR=1.73 for one parent smoker RR=2.60 for two parent smokers	7.6 10.3	10.4 15.1	11.1 14.5	15.2 23.2	= Asymptomatic parents = Symptomatic parents Neither controlled for sibling number or smoker sex Longitudinal study
Fergusson et al. (1981); Fergusson and Horwood (1985)[2]	1,286 births, 4 months, 1977, New Zealand	Questionnaire, doctor or hospital visits, bronchitis/pneumonia; hospital records checked; assessed at 4 months, 1, 2, 3. and 6 years; RR=2.04 if mother smoked	7.0 7.0	12.8 4.6	13.4 8.8	Maternal only Paternal only	Effect significant for maternal smoking in first year of life only; effect present in first 2 years of life
			By number of smoking parents				
			0	1	2		
Were et al. (1984)	8,528 children, aged 5-9, with two perents' smoking status known, six U.S. cities	Respiratory illness in last year	12.9	13.7	14.8		Adjusted for age, sex, and city cohort effect; significant trends Longitudinal study

TABLE 1.—Continued

Study	Subjects	Findings	Illness rates per 100			Comments
Said et al. (1978)	3,920 children, aged 10–20, France	Tonsillectomy and/or adenoidectomy, generally before age 5, as indicator of frequent respiratory tract infection	28.2	41.4	50.9	Children self-reported; not clear parent smoking habit at report time directly related to exposure approx. 10+ years earlier Cross-sectional study
Schenker et al. (1983)	4,071 children, aged 5–14, United States	Chest illness before age 2 Chest illness >3 days in past year	6.7 8.8	7.9 11.8	11.5 13.6	Trends for both significant Cross-sectional study
			Parent status			
			Nonsmoker	Current smoker		
Cameron et al. (1969)	158 children, aged 6–9; parents' telephone questionnaire, United States	Respiratory illness, restricted activity and/or medical consultation in last year	1.33	7.4		Illness reported not verified; not clear how reporting adult related to child Cross-sectional study
Leeder et al. (1976a, b)	2,149 infants, born 1963–1965, England	RR ~ 2.0 for infants with two smoking parents	Not provided			Parents' response bias unlikely, effects observed for infants of asymptomatic parents; maternal vs. paternal smoking effects not investigated Longitudinal study
Sims et al. (1978)	35 children, hospitalized, RSV bronchiolitis; 35 controls, England	Borderline significant increase in maternal smoking, first year of life RR=2.65	Not provided			No significant effect for paternal smoking; average amount smoked greater for parents of cases than controls Case-control study

TABLE 1.—Continued

Study	Subjects	Findings	Illness rates per 100			Comments
Rantakallio (1978)	1,821 children of smoking mothers, 1,823 children of nonsmoking mothers, Finland	Significant increase in hospitalization for respiratory illness during first 5 years of life RR=1.74	Not provided			Prospective followup of doctor visits, hospitalizations, deaths up to age 5; only maternal smoking evaluated Longitudinal study
Pullan and Hey (1982)	130 children hospitalized, RSV infection, first year of life; 111 nonhospitalized controls, England	Significant effect of maternal (RR=1.96) and paternal (RR=1.53) smoking at time of study; significant maternal smoking effect during first year of life (RR=1.55)	Not provided			Case-control study
				Nonsmoker	Smoker	
Pedreira et al. (1985)	1,144 infants in pediatric practice, United States	Significant increase in respiratory illnesses among smoke-exposed children	Bronchitis	71	103	Pediatricians not blinded to exposure; no effect seen for croup, pneumonia, or bronchiolitis Longitudinal study
			Tracheitis	21	40	
			Laryngitis	4	7	

[1] These data are considered in a more expanded analysis provided by Leeder et al. (1976a, b).

[2] Relative risk for children of smoking mothers versus children of nonsmoking mothers calculated from data provided by J.M. Samet (personal communication).

of nonsmoking mothers. In addition, they demonstrated a dose-response relationship between the amount of maternal smoking and the number of hospital admissions for these conditions. The infants were classified by the mothers' prenatal smoking behavior and not by the mothers' smoking behavior during the first year of the child's life. Maternal smoking habits would probably have remained relatively stable across the short observation period.

British investigators (Colley et al. 1974) followed children born between 1963 and 1965 in London and also observed an increased frequency of bronchitis and pneumonia during the first year of life in the children of parents who smoked. This difference did not persist at 2 to 5 years of age. This effect was independent of the parents' personal reports of winter morning phlegm and increased with the amount of smoking by parents. The annual incidence of bronchitis and pneumonia during the first year of life also increased with a greater number of siblings. This variable was not controlled in the original analysis however, Leeder and colleagues (1976b) subsequently reported that, in this same cohort, a dose-response relationship with parental smoking persisted for bronchitis and pneumonia in the first year of life, after control for parental respiratory symptoms, the sex of the child, the number of siblings, and a history of respiratory illness in the siblings.

Fergusson and colleagues (1981) studied 1,265 New Zealand children from birth to age 3. They demonstrated an increase in bronchitis and pneumonia and in lower respiratory illness during the first 2 years of life in children whose mothers smoked compared with children whose mothers did not smoke. Correction for maternal age, family size, and socioeconomic status did not affect the relationship between the amount of maternal smoking and the rate of respiratory illness. The effect of maternal smoking declined with increasing age of the child.

In a second report (Fergusson and Horwood 1985) the followup was extended to include the first 6 years of life. The results confirmed the initial findings. Maternal, but not paternal, smoking was associated with a statistically significant increase in lower respiratory illnesses during the first 2 years of life. However, after age 2 there was no significant effect of maternal smoking on respiratory illness occurrence.

Rantakallio (1978) followed more than 3,600 children during the first 5 years of life; half of the children had mothers who smoked cigarettes during pregnancy and half did not. The children of mothers who smoked had a 70 percent greater chance of hospitalization for a respiratory illness than the children of nonsmoking mothers.

Pedreira and associates (1985) prospectively studied 1,144 infants and their families in the greater Washington, D.C., area. Maternal

smoking was associated with an excess frequency of acute bronchitis, tracheitis, and laryngitis, as diagnosed by the pediatricians caring for these families. Episodes of croup, pneumonia, and bronchiolitis were not increased by maternal smoking. A family history of chronic respiratory symptoms was also associated with excess respiratory illness.

Ware and coworkers (1984) studied more than 10,000 children in six American cities. Maternal cigarette smoking was associated with increased parental reporting of a doctor-diagnosed respiratory illness before the age of 2 years and of an acute respiratory illness within the past year. The prevalence of positive questionnaire responses increased consistently with the current daily cigarette consumption of the mother; the dose-response relationships were unchanged by adjustment for maternal symptoms and educational status.

Cross-Sectional Studies

Schenker and coworkers (1983) studied 4,071 children between the ages of 5 and 14 years in a cross-sectional study in Pennsylvania. Both chest illness in the past year and severe chest illness before age 2 were more frequently reported in nonsmoking children of parents who smoked. These investigators found that symptom and illness rates were higher in children of parents with respiratory symptoms. However, a significant effect of maternal smoking on these illness variables remained after adjustment for the parents' own respiratory symptom history.

In a study of 1,355 children between 6 and 12 years of age in the Iowa public schools, Ekwo and coworkers (1983) found that the presence in the home of at least one parent who smoked was significantly associated with reported hospitalization of the child for a respiratory illness during the first 2 years of life. As in other studies, the effect was stronger for maternal smoking than for paternal smoking.

Case-Control Studies

In England, Sims and colleagues (1978) examined 35 children at 8 years of age who had been hospitalized during infancy for RSV bronchiolitis and compared them with 35 control children of similar age. Maternal smoking was associated with a relative risk of 2.65 for hospitalization due to bronchiolitis. The sample size was small, and this effect of maternal smoking was not statistically significant.

Pullan and Hey (1982) studied children who had been hospitalized with documented RSV infection in infancy. They found significantly greater smoking by their mothers at the time of the infection, compared with children hospitalized for other illnesses, including respiratory disease for which RSV infection was not documented. At

age 10, the children previously ill with RSV infection had an excess reported occurrence of wheeze and asthma and had lower levels of pulmonary function in comparison with the controls. The researchers could not determine whether the RSV infection had caused persistent damage that affected the maturation of the lung or whether these children were already more susceptible to severe RSV infection because of pulmonary problems that antedated the RSV infection.

In summary, the results of these studies show excess acute respiratory illness in the children of parents who smoke, particularly in children under 2 years of age. This pattern is evident in studies conducted with different methodologies and in different locales. The increased risk of hospitalization for severe bronchitis or pneumonia associated with parental smoking ranges from 20 to 40 percent during the first year of life. Young children appear to represent a more susceptible population for the adverse effects of involuntary smoking than older children or adults. The time-activity patterns of infants, which generally place them in proximity to their mothers, may lead to particularly high exposures to environmental tobacco smoke if the mother smokes.

Acute respiratory illnesses during childhood may have, long-term effects on lung growth and development, and might increase the susceptibility of the lung to the effects of active smoking and to the development of chronic obstructive lung disease (Samet et al. 1983; US DHHS 1984).

Cough, Phlegm, and Wheezing

A number of cross-sectional studies from different countries (Table 2) have shown a positive association between parental cigarette smoking and the prevalence of chronic cough and chronic phlegm in children; some studies have shown a relationship for persistent wheeze. However, not all studies have shown a positive relationship for all symptoms. The results of some of these studies may have been confounded by the child's own smoking habits (Colley et al. 1974; Bland et al. 1978; Kasuga et al. 1979). The association with parental smoking was not statistically significant for all symptoms in all studies (Lebowitz and Burrows 1976; Schilling et al. 1977; Schenker et al. 1983). However, the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking parents in the home.

A recent report (Charlton 1984) provides cross-sectional data on parent-reported cough for 15,000 children, 8 to 19 years of age, in northern England. Chronic cough in the children was related to their age and to their own cigarette smoking status. However, with control of these factors by stratification, the number of parental smokers in the home was positively associated with the occurrence of chronic

TABLE 2.--Chronic respiratory symptoms in children in relation to involuntary smoke exposure

Study	Subjects	Respiratory symptoms or illness	Rates per 100 by number of smoking parents			Comments
			0	1	2	
Colley et al. (1974)	2,426 children, aged 6-14, England	Chronic cough; questionnaire completed by parent	15.6	17.7	22.2	Trend significant; reporting bias possible result of parent symptoms or active smoking in children, unlikely to explain full effect of trend Cross-sectional study
Bland et al. (1978)	3,105 children, aged 12-13, did not admit to ever smoking cigarettes, England	Cough during day or at night	16.4	19.0	23.5	Children's self-reported symptoms and smoking history collected simultaneously; morning and daytime cough suggested an different diseases, could be difference in exposure (exposure more likely awake than asleep) (Cross-sectional study, adjusted for child's own smoking habits
		Morning cough	1.5	2.8	2.9	
Weiss et al. (1980)	650 children, aged 5-9, United States	Chronic cough and phlegm	1.7	2.7	3.4	Trend not significant
		Persistent wheeze	1.8	6.8	11.8	Trend significant Cross-sectional study, adjusted for parental symptoms and child's own smoking
Charlton (1984)	15,000 children, aged 8-19 years, England	**Any cough**	40.0	45.0	55.0	Trend significant; percents not age adjusted Cross-sectional study, adjusted for child's own smoking, not parental symptoms

TABLE 2.—Continued

Study	Subjects	Respiratory symptoms or illness	Rates per 100 by number of smoking parents: 0	1	2	Comments
Dodge (1982)	628 children, grades 3–4, two-parent households; parent questionnaire response, United States	Any wheeze	27.6	27.9	40.0	All trends significant; some effect might relate to parental symptoms, but no trend influence likely Cross-sectional study
		Phlegm	6.4	10.9	12.0	
		Cough	14.6	23.0	27.8	
Schenker et al. (1983)	4,071 children, aged 5–14, United States	Chronic cough	6.2	7.0	8.3	Trend not significant; not adjusted for parental symptoms, although parental symptom effect analyzed Cross-sectional study
		Chronic phlegm	4.1	4.8	4.0	
		Persistent wheeze	7.2	7.7	5.4	
			Never smoker		Parent smoker	
Lebowitz and Burrows (1976)	1,525 children, <15 years old, United States	Persistent cough	3.7		7.2	Higher rates in symptomatic parent households; trends persisted for asymptomatic households; no adjustment for child's own smoking Cross-sectional study
		Persistent phlegm	10.0		12.8	
		Wheeze	23.4		24.1	
Schilling et al. (1977)	816 children, age 7+, United States	Cough, phlegm, wheeze	No significant effect			Specific data not provided Cross-sectional study
Kasuga et al. (1979)	1,937 children, aged 6–11, Japan	Wheeze, asthma	Increased prevalence in heavy smoker (>21 cig/day) family; less clear effect in light smoker (<21 cig/day) family			Adjusted for distance of home from main traffic, highway Cross-sectional study
Ekwo et al. (1983)	1,355 children, aged 6–12, United States	Coughs with colds	Odds ratios: 1.4 for smoker father, 1.5 for smoker mother			Gas stove use measured, not controlled for; no consistent dose-response Cross-sectional study
		Wheezing apart from colds	2 if only smoker mother			

cough. The mother's smoking had a greater effect than the father's smoking.

Burchfiel and colleagues (1986) have conducted a longitudinal study of 3,482 subjects from Tecumseh, Michigan. Subjects were initially between the ages of birth and 10 years and were followed up by questionnaire and examination 15 years after entry into the study. Age-specific incidence rates were calculated for a number of chronic respiratory symptoms, including cough, phlegm, wheeze, and bronchitis. Incidence rates for all symptoms were higher for children with two parental smokers when compared with children of non-smokers. Adjustment for potential confounding variables, including age, parental education, family size, and personal smoking, did not explain these results.

British researchers (Leeder et al. 1976b) studying a birth cohort over a 5-year period demonstrated an increased incidence of wheezing among nonasthmatic children with two parents who smoked in comparison with children whose parents did not smoke, one parent who smoked, or parents whose smoking changed during the study (Leeder et al. 1976a). However, when this association was examined by logistic regression with control for other factors, parental smoking was not a significant predictor of wheeze or of asthma.

McConnochie and Roghmann (1984) performed a retrospective cohort study to examine the influence of mild bronchitis in early childhood on wheezing symptoms 8 years later when the subjects had reached a mean age of 8.3 years. Involuntary smoking was a significant predictor of current wheezing (odds ratio 1.9). In a related study (McConnochie and Roghmann 1985) with these same children, involuntary smoking did not affect lower respiratory tract illness experience.

In a study of 650 children aged 5 to 10 years (Weiss et al. 1980), a significant trend in the reported prevalence of chronic wheezing with current parental smoking was found; the rates were 1.9 percent, 6.9 percent, and 11.8 percent for children with zero, one, and two parents who smoked, respectively. Although the data given are for all households, when the analysis was restricted to those households where neither parent reported symptoms, the results were identical. The stability of the findings with this restriction suggests that reporting bias introduced by parental symptoms was not responsible for the observed results.

Schenker and coworkers (1983) examined the influence of parental smoking and symptoms on the reporting of chronic respiratory symptoms of cough, phlegm, and persistent wheezing in children. These investigators found that the mothers were more likely than the fathers and symptomatic mothers were more likely than asymptomatic mothers to report these symptoms in their children.

Parental smoking had no significant effects on chronic respiratory symptoms.

Lebowitz and Burrows (1976) assessed the effects of household members' smoking on respiratory symptoms in 626 Tucson children younger than 15 years of age. Children from homes with current smokers had higher symptom rates than those from homes with ex-smokers and with never smokers. However, the effect of household smoking type was statistically significant only for persistent cough. In a general population study, Schilling and colleagues (1977) reported no association between wheeze and involuntary smoking.

Ware and associates (1984) enrolled 10,106 children between 6 and 9 years of age from six U.S. cities in a prospective study. The prevalence of persistent cough and persistent wheeze, measured at the second examination, was higher in children whose parents smoked. The effect was greater for maternal smoking than for paternal smoking. Symptom prevalence rates increased linearily with the number of cigarettes smoked daily by the mother. In a multiple logistic model, the effect of maternal smoking persisted after adjustment for reported illness in the parents.

Dodge (1982), studying third and fourth grade children in Arizona, found that symptoms, including wheeze, were related to both the presence of symptoms in the parents and the number of smokers in the household.

In summary, children whose parents smoke had a 30 to 80 percent excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. Many studies showed an exposure-related increase in the percentage of children with reported chronic symptoms as the number of parental smokers in the home increased. Misclassification as nonsmokers of children who are actively smoking could bias the results of these studies. Adolescent smokers may be reluctant to accurately report their smoking habits, and more objective measures of exposure may not help to distinguish active experimentation with cigarettes from involuntary exposure to smoke (Tager 1986). Although misclassification of children who are actively smoking as nonsmokers must be considered, many studies showing a positive association between parental smoking and symptoms in children, including children at ages before significant experimentation with cigarettes is prevalent. In addition, many studies (Bland et al. 1978; Weiss et al. 1980; Charlton 1984; Schenker et al. 1983; Dodge 1982; Burchfiel et al. 1986) found significant effects of parental smoking after considering active smoking by the children.

Chronic respiratory symptoms represent an immediate health burden for the child. However, the long-term significance of chronic respiratory symptoms for the health of the child is unclear. Most

available data are cross-sectional, and followup studies of chronically symptomatic children are necessary to determine the long-term health consequences of chronic respiratory symptoms.

Pulmonary Function

In recent years, the effect of parental cigarette smoking on pulmonary function in children has been examined in cross-sectional studies (Table 3) and a few longitudinal studies. The cross-sectional studies have demonstrated lower values on tests of pulmonary function ($FEV_{75\%}$, FEV_1, FEF_{25-75}, and flows at low lung volumes) in children of mothers who smoked compared with children of non-smoking mothers. The longitudinal studies (Table 4) have confirmed the cross-sectional results and provide some insight into the implications of the cross-sectional data.

Dose-response relationships have been found in both cross-sectional and longitudinal studies (Tager et al. 1979; Weiss et al. 1980; Ware et al. 1984; Berkey et al. 1986); the level of function decreases with an increasing number of smokers in the home. As would be anticipated from the mother's greater contact time with the child, maternal smoking tends to have a greater impact than paternal smoking. Younger children seem to experience greater effects than older children (Tager et al. 1979; Weiss et al. 1980), and in older children the effects of personal smoking may be additive with those of involuntary smoking (Tager et al. 1979, 1985).

As noted by Tager (1986), the effect of maternal smoking on lung function may vary with the child's sex. Some studies have reported greater effects on flows at lower lung volumes in girls than in boys (Burchfiel et al. 1986; Tashkin et al. 1984; Yarnell and St. Leger 1979; Vedal et al. 1984). Flows at higher lung volumes seem more affected in boys (Burchfiel et al. 1986; Yarnell and St. Leger 1979; Berkey et al. 1986; Tashkin et al. 1984). Whether these sex effects represent differences in exposure, differences in susceptibility to environmental cigarette smoke, or differences in growth and development is unclear.

Tager and colleagues (1983) followed 1,156 children for 7 years to determine the effect of maternal smoking on the growth of pulmonary function in children (Figure 2). After correcting for previous level of FEV_1, age, height, personal cigarette smoking, and correlation between mother's and child's pulmonary function level, maternal smoking was associated with a reduced annual increase in FEV_1 and FEF_{25-75}, using two separate methods of analysis. If the effect of maternal smoking is maintained to 20 years of age, then a 3 to 5 percent reduction of FEV_1 and FEF_{25-75} due to maternal smoking would be projected. The validity of this projection remains to be established. Because few mothers changed their smoking habits, the

TABLE 3.—Pulmonary function in children exposed to involuntary smoking

Study	Subjects	Pulmonary function measured	Outcome	Comments
Schilling et al. (1977)	816 children, aged 7–17, Connecticut and South Carolina, United States	FEV_1 as percent predicted	No effect of parental smoking	No control for sibship size or correlation of sibling pulmonary function; for children who never smoked, V_{max50} significantly less in children with smoking mothers
Tager et al. (1979)	444 children, aged 5–19, East Boston, Massachusetts, United States	MMEF in standard deviation units	Significant effect of parental smoking	Controlled for sibship size and correlation of sibling pulmonary function
Weiss et al. (1980)	650 children, aged 5–9, East Boston, Massachusetts, United States	MMEF in standard deviation units	Significant effect of parental smoking	Controlled for sibship size and correlation of sibling pulmonary function
Vedal et al. (1984)	4,000 children, aged 6–13, United States	FEV_1, FVC, $\dot{V}_{max50}$, $\dot{V}_{max75}$, V_{max90}	FVC positively associated, flows negatively associated	Flows dose–response with amount smoked by mother
Lebowitz and Burrows (1976)	271 households, complete histories of parent smoking and pulmonary function of children, age >6, Tucson, Arizona, United States	FEV_1, FVC, $\dot{V}_{max50}$, $\dot{V}_{max75}$ derived from MMEF V curves, as standard deviation units	No effect of parental smoking	Suggestion: may be real differences in indoor levels of exposure compared with more northerly climates
Lebowitz et al. (1982)	229 children, Tucson, Arizona, United States	FEV_1, z score	No effect of parental smoking	Higher levels of pulmonary function for children of smoking parents than for non-smoke-exposed children

TABLE 3.—Continued

Study	Subjects	Pulmonary function measured	Outcome	Comments
Dodge (1982)	558 children, aged 8–10, Arizona, United States	FEV_1 by age change FEV_1/H^3/year	No effect of parental smoking	Potential participation rate bias; cross-sectional data not controlled for child height; annual FEV_1/H^3 at ages 8, 9, and 11 consistently greater in nonsmoking households than two-parent smoker households; statistical test not significant
Tashkin et al. (1984)	1,080 nonsmoking, nonasthmatic children, Los Angeles, United States	$\dot{V}_{max}$, $\dot{V}_{max75}$, $\dot{V}_{max25}$, FEF_{25-75}	Decreased $\dot{V}_{max}$, $\dot{V}_{max25}$ for boys, and FEF_{25-75}, $\dot{V}_{max75}$ for girls with smoking mother at least	No effect of paternal smoking
Chen and Li (1986)	571 children, aged 8–16, China	FEV_1 and MMEF	Significantly decreased FEV_1 and MMEF in children exposed to paternal cigarette smoke	Adjusted for child's own smoking, gas stoves, and parental symptoms
Hasselblad et al. (1981)	16,689 children, aged 5–17, seven geographic regions, United States	FEV_1 as percent predicted	Significant effect of maternal but not paternal smoking	Large number of children excluded for invalid pulmonary function data or missing parental smoking data
Speizer et al. (1980)	8,120 children, aged 6–10, six U.S. cities	FVC and FEV_1 as percent predicted	No effect for FEV_1 or FVC	Recent analysis demonstrated an effect for FVC and FEV_1
Lebowitz (1984)	117 families, Tucson, Arizona, United States	FVC and FEV_1	No effect of parental smoking	Also assessed, TSP and ozone rates had little effect
Ekwo et al. (1983)	1,355 children, aged 6–12, Iowa City, Iowa, United States	FEV_1, FVC	No effect of parental smoking	Data for this outcome not specifically analysed; increased bronchial responsiveness among smoke-exposed children
Spinaci et al. (1985)	2,385 schoolchildren, Turin, Italy	FEV_1	Statistically significant effect of maternal smoking	No passive smoking effect difference between boys and girls

TABLE 4.--Pulmonary function in children exposed to involuntary smoking; longitudinal studies

Study	Subjects	Pulmonary function measured	Outcome	Comments
Tager et al. (1983)	1,156 children, aged 5-10 at initial survey, East Boston, Massachusetts, United States	FEV_1, FEF_{25-75}	Significantly decreased FEV_1 and FEF_{25-75} growth rate for children of smoking mothers	7-year followup; no effect of paternal smoking; magnitude roughly 4 to 5 percent
Ware et al. (1984)	10,000 children, aged 6-11, six U.S. cities	FVC, FEV_1	FVC positively associated with smoking; FEV_1 negatively associated with smoke exposure	FEV_1 dose-response with amount smoked by mother; magnitude of effect estimate 6 percent
Berkey et al. (1986)	7,334 children, aged 6-10, six U.S. cities	FVC, FEV_1	Slightly higher FVC level, slightly lower FEV_1 level in smoke-exposed; growth of both decreased by smoke exposure	Consistent with 3 percent deficit in FEV_1 growth
Burchfiel et al. (1986)	3,432 children, aged 0-10, Tecumseh, Michigan, United States	FVC, FEV_1, V_{max50}	FEV_1 level and growth decreased by maternal smoking	Dose-response in male children with number of parental smokers

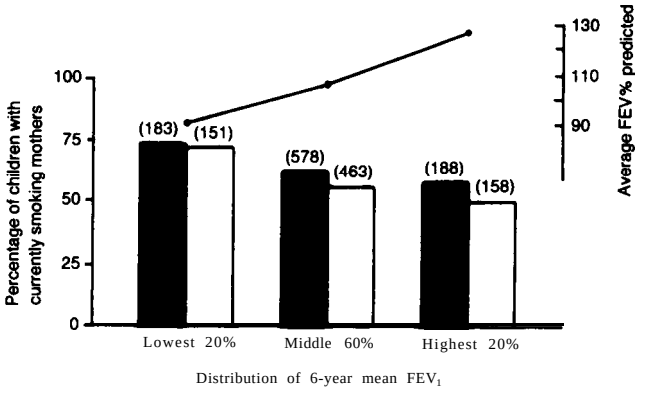

FIGURE 2.--Percentage of children with mothers who were current cigarette smokers at initial examination (black columns) and sixth examination (white columns), according to distribution of mean age, height, and sex-corrected FEV_1 over the first six examinations

Noted: Lowest 20%, middle 60%, and highest 20% refer to children with values in the bottom one-fifth, middle three-fifths. and upper one-fifth. respectively, of the mean FEV_1 distribution; numbers in parentheses indicate number of children in each group; the three circles represent the average percent predicted values of FEV_1 for the three groups; results for male and female children were combined, because difference between sexes was not significant.

SOURCE: Tager et al. (1983).

study could not establish the ages at which children were most vulnerable to exposure to tobacco smoke.

Ware and colleagues (1984) followed 10,106 white children for two successive annual examinations as part of the Harvard Air Pollution Health Study in six U.S. cities. The forced vital capacity was significantly higher for children of mothers who were either current smokers or ex-smokers. However, children whose mothers were current smokers had a 0.6 percent lower mean FEV_1 at the first examination and 0.9 percent lower mean FEV_1 at the second examination. Maternal smoking had a greater effect than paternal smoking, although the effects of both were significant. The changes in level of FEV_1 observed were small. For exposure to a mother who smoked one pack of cigarettes per day, the FEV_1 was estimated to be decreased by less than 1 percent, or 10 to 20 mL for a child with an FEV_1 between 1.5 and 2.5 liters. Projecting the effect cumulatively to age 20 yields an approximately 3 percent deficit. This effect is comparable to that observed by Tager and colleagues (1983). These small average effects may underestimate the effects on populations of susceptible children.

A more extensive analysis of longitudinal data from the Harvard cohort was performed using a mathematical model to describe lung growth (Berkey et al. 1986). This analysis included 7,834 children between 6 and 10 years of age who were evaluated from two to five times over a 5-year period. The model estimated that a smoke-exposed child at age 8 would have an $FEV_1$0.81 percent lower than a non-smoke-exposed child, and growth of FEV_1 would be 0.17 percent lower per year. Both effects were statistically significant. For an 8-year-old child with an FEV_l of 1.62 liters, these results translate into a deficit of 13 mL in FEV_1 and of 3 mL in annual increase in FEV_l. The magnitude of the maternal smoking effect is consistent with a deficit in FEV_l of 2.8 percent in naturally attained growth, if the effect is sustained throughout childhood.

Burchfiel and colleagues (1986) have conducted a longitudinal study of 3,482 children observed over a 15-year period in Tecumseh, Michigan. The mean increase in FEV_l for nonsmoking boys between the ages of 10 and 19 years was 82.3, 76.2, and 74.5 mL per year for subjects with zero, one, and two smoking parents, respectively. Boys with one parent who smoked experienced 92.6 percent and boys with two parents who smoked experienced 90.5 percent of the growth in FEV_l seen in male children with nonsmoking parents. Effects of parental smoking were not found in girls.

The available data demonstrate that maternal smoking reduces lung function in young children. However, the absolute magnitude of the difference in lung function is small on average. A small reduction of function, on the order of 1 to 5 percent of predicted value, would not be expected to have functional consequences. However, some children may be affected to a greater extent, and even small differences might be important for children who become active cigarette smokers as adults.

A minority of adult cigarette smokers develop chronic obstructive lung disease, and factors influencing lung growth and development during childhood might predispose to disease in adulthood (Samet et al. 1983; Speizer and Tager 1979). In Figure 3 is depicted a model of growth and decline in pulmonary function from childhood through adulthood, as measured by the FEV_1. Pulmonary function peaks in early adult life and declines steadily thereafter in both smokers (curve B) and nonsmokers (curve A). In people who develop chronic lung disease (curve C), a more rapid decline has occurred. Childhood factors could predispose to the development of disease by reducing the functional level at which decline begins or by increasing susceptibility to cigarette smoke and increasing the rate of decline. Thus, in this model, small decrements in the maximally attained level of pulmonary function may be important in identifying the susceptible smoker. However, the prerequisite longitudinal studies needed to test this hypothesis have not yet been conducted.

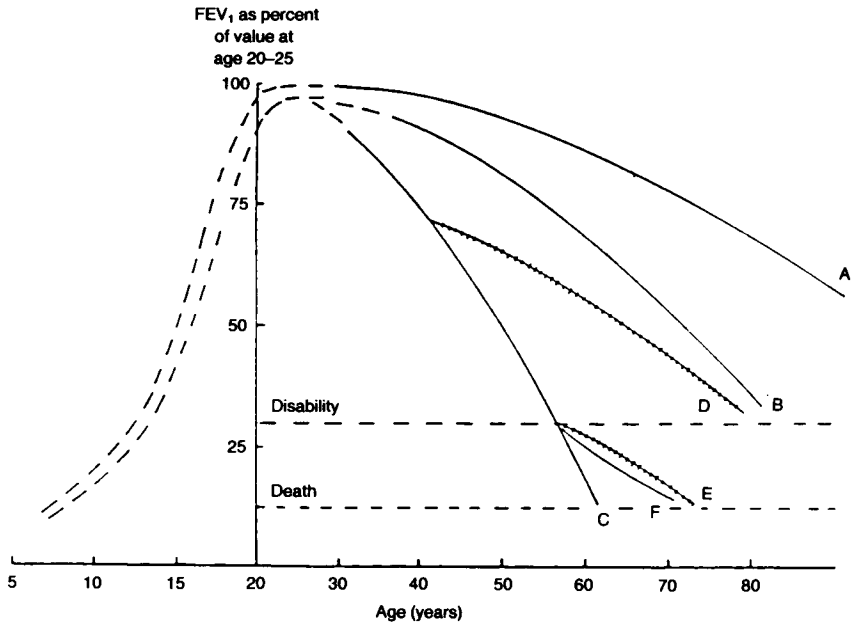

FIGURE 3.—Theoretical curves representing varying rates of change in FEV_1 by age

NOTE: Curve A, normal decline in FEV_1 (forced expiratory volume in 1 second); curve B, accelerated decline in FEV_1 with cigarette smoking; curve D, the effect of smoking cessation, also seen in disabled individuals (curve E); disability-related decline often continues as a variable rate (curves C and F).

SOURCE: Speizer and Tager (1979).

Bronchoconstriction

Nonspecific bronchial responsiveness has been considered a potential risk factor for the development of chronic obstructive lung disease in both adults and children (US DHHS 1984). This physiologic trait may be influenced by environmental exposures such as involuntary smoking by children and active smoking by adults, and by respiratory infections at all ages.

Asthma is a chronic disease characterized by bronchial hyperresponsiveness. Epidemiologic studies of children have shown no consistent relationship between the report of a doctor's diagnosis of asthma and exposure to involuntary smoking. Although one study showed an association between involuntary smoking and asthma (Gortmaker et al. 1982), others have not (Schenker et al. 1983; Horwood et al. 1985). This variability may reflect differing ages of the children studied, differing exposures, or uncontrolled bias. In several recent studies (Murray and Morrison 1986; O'Connor et al.

1986; Weiss et al. 1985; Martinez et al. 1985; Ekwo et al. 1983), nonspecific bronchial responsiveness was examined in relationship to involuntary smoking. The results of these studies suggest that exposure to maternal cigarette smoking is associated with increased nonspecific airways responsiveness. Some reports suggest that the increased responsiveness is present only in children known to be asthmatic (Murray and Morrison 1986; O'Connor et al. 1986), whereas others suggest that the increased responsiveness is seen in all children (Ekwo et al. 1983; Martinez et al. 1985). The pathophysiological mechanisms underlying the increased responsiveness and the long-term consequences of the increased responsiveness remain unknown. This section reviews the studies on asthma and on bronchial hyperresponsiveness.

Gortmaker and coworkers (1982) studied the relationship between parental smoking and the prevalence of asthma in children up to 17 years of age. Random community-based populations in Michigan (3,072 children) and Massachusetts (894 children) were surveyed. Parents reported on their own smoking habits and on the asthma histories of their children. Biased reporting by parents who smoked was assessed by examining the relationship between parental smoking and other conditions, and considered not to be present. Asthma prevalence declines with age, and asthmatic children are unlikely to tolerate active smoking; therefore, misclassification of actively smoking asthmatic children as nonsmokers seems unlikely. In comparison with children of nonsmokers, children whose parents smoked were more likely to have asthma (relative risks of 1.5 and 1.8 for Michigan and Massachusetts children, respectively) and severe asthma (relative risks of 2.0 and 2.4, respectively). The investigators estimated that between 18 and 23 percent of all childhood asthma and 28 and 34 percent of severe childhood asthma is attributable to exposure to maternal cigarette smoke.

Schenker and coworkers (1983) studied 4,071 children between 5 and 15 years of age in western Pennsylvania. These investigators found no relationship of parental smoking to the occurrence of asthma, after adjustment for potential confounding factors.

Horwood and coworkers (1985) conducted a cohort study of 1,056 children in New Zealand who were followed from birth to age 6 years. A family history of allergy and male sex were the only significant predictors of incident cases of asthma. Neither parental smoking nor respiratory illnesses were predictive of the occurrence of asthma in this investigation.

A recently reported cross-sectional study by Murray and Morrison (1986) suggests a mechanism by which maternal cigarette smoking might influence the severity of childhood asthma. These investigators studied 94 children, aged 7 to 17 years, with a history of asthma. The children of mothers who smoked had 47 percent more symp-

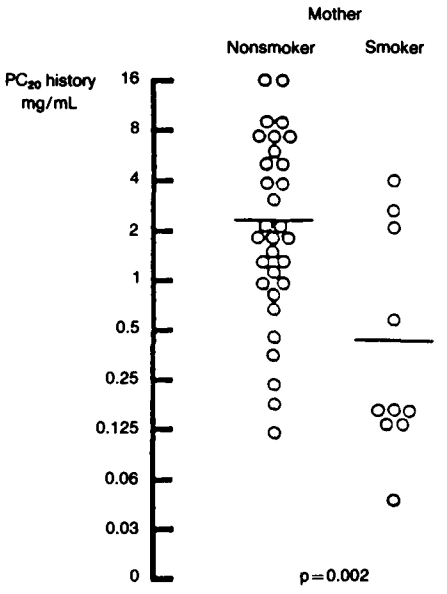

FIGURE 4.—PC_{20} in two groups of children with a history of wheezing

NOTE: Mothers of 32 were nonsmokers; mothers of 10 were smokers.
SOURCE: Murray and Morrison (1986).

toms, a 13 percent lower FEV_1, and a 23 percent lower FEF_{25-75} than the children of nonsmoking mothers. Forty-one children, who had been able to discontinue medication and had no recent respiratory illness, underwent a histamine challenge test. There was a fourfold greater responsiveness to histamine among the asthmatic children of mothers who smoked (Figure 4) compared with asthmatic children of nonsmoking mothers. Dose-response relationships were present for all outcome variables in this study: symptoms, pulmonary function, and airways responsiveness. The differences between children of smoking mothers and children of nonsmoking mothers were greatest in the older children. The father's smoking behavior did not influence the child's asthma severity. The sample of asthmatic children with mothers who smoked was small (N = 10), and only 41 of 96 children had histamine challenge tests. Given the heterogeneity of asthma, the variable nature of bronchial hyperreactivity in asthma, and the potential for biased selection, these results must be interpreted with caution.

O'Connor and coworkers (1986) studied 286 children and young adults, 6 to 21 years of age, drawn from a community-based sample,

and confirmed the findings of Murray and Morrison (1986). Bronchial responsiveness was measured with eucapneic hyperpnea to subfreezing air. Among the 265 subjects without asthma there was no significant relationship between maternal cigarette smoking and nonspecific bronchial responsiveness. However, in the 21 subjects with active asthma, maternal smoking was significantly associated with increased levels of bronchial responsiveness.

In a study of 1,355 children 6 to 12 years of age, significant increases in FEV and FEF_{25-75} were observed following isoproterenol administration in children whose parents smoked (Ekwo et al. 1983). Increases after isoproterenol were not observed in children of nonsmoking parents.

Weiss and coworkers (1985) evaluated 194 subjects between the ages of 12 and 16 drawn from the same population as those reported by O'Connor and coworkers (1986), with eucapneic hyperpnea to subfreezing air as a test for bronchial responsiveness and allergy skin tests as a test for atopy. Subjects defined as atopic (any skin test wheal greater than or equal to 5 mm) had twice the frequency of lower respiratory illnesses in early childhood and were twice as likely to have a mother who smoked. However, there was no relationship between maternal smoking and increased bronchial responsiveness.

Martinez and associates (1985) studied 170 9-year-old children in Italy. Nonspecific bronchial responsiveness to methacholine and allergy prick test positivity in these subjects was significantly associated with maternal cigarette smoking.

These data suggest that maternal cigarette smoking may influence the severity of asthma; a mechanism for this effect may be through alteration of nonspecific bronchial responsiveness. Further investigation is needed to determine whether exposure to environmental cigarette smoke can induce asthma in children and whether ETS exposure increases the frequency or severity of attacks of bronchoconstriction in asthmatics. The effect of involuntary smoking on increased bronchial responsiveness in asthmatics and in nonasthmatics has only recently been addressed. These initial data are provocative, but the magnitude of the effect, the target population at risk, the underlying mechanisms, and the long-term consequences have not been described. Furthermore, the complex interrelationships among respiratory illness, atopy, parental smoking, and airways responsiveness have not been clarified and require further study.

Ear, Nose, and Throat

Five studies (Said et al. 1978; Iverson et al. 1985; Kraemer et al. 1983; Black 1985; Pukander et al. 1985) show an excess of chronic

middle ear effusions and diseases in children exposed to parental smoke.

Said and colleagues (1978) questioned 3,920 children between 10 and 20 years of age about prior tonsillectomy or adenoidectomy, considered an index of frequent upper respiratory or ear infections. The investigators reported that, in general, this surgery was performed before the children were 5 years old. The prevalence of prior surgery increased with the number of currently smoking parents in the home.

Iverson and coworkers (1985) prospectively studied 337 children enrolled in all day-care institutions in a municipality over a 3-month period to evaluate the importance of involuntary smoking for middle ear effusion in children. Middle ear effusion was assessed with tympanometry, and the overall prevalence was found to be approximately 23 percent. Although various indoor environmental factors were assessed in this investigation, only parental smoking was significantly associated with middle ear effusion. The effect of parental smoking persisted with control for the number of siblings. The overall age-adjusted odds ratio was 1.6 (95 percent confidence interval 1.0-2.6). In 5- to 7-year-old children, 10 to 36 percent of all chronic middle ear effusions could thus be attributed to smoking on the basis of these results.

Kraemer and coworkers (1983) performed a case-control study of 76 children to examine the relationship of environmental tobacco smoke exposure to the occurrence of persistent middle ear effusions. Frequent ear infections, nasal congestion, environmental tobacco smoke exposure, and atopy were all more frequent in children with ear effusions. The effect of involuntary smoking was observed only if nasal congestion was present, and was greatest in children who were atopic.

Black (1985) performed a case-control study of glue ear with 150 cases and 300 controls. Parental smoking was associated with a relative risk of 1.64 (95 percent C.I. 1.03-2.61) for glue ear. In Finland, Pukander and coworkers (1985) conducted a case-control study of 264 2- to 3-year-old children with acute otitis media and 207 control children and found an association between parental smoking and this acute illness.

These studies are consistent in their demonstration of excess chronic middle ear effusions, a sign of chronic ear disease, in children exposed to parental cigarette smoke. Potential confounding factors for middle ear effusions should be examined carefully in future studies. The long-term implications of the excess middle ear problems deserve further study.

Adults

Acute Respiratory Illness

There are no studies of acute respiratory illness experience in adults exposed to environmental cigarette smoke.

Cough, Phlegm, and Wheezing

Few studies have addressed the relationship of chronic respiratory symptoms in nonsmoking adults with environmental tobacco smoke exposure. Schilling and colleagues (1977) found that symptoms in adult men and women were related to personal smoking habits and that the occurrence of cough, phlegm, or wheeze in nonsmokers was not related to the smoking habits of their spouses. Schenker and colleagues (1982) confirmed these results in a telephone survey of 5,000 adult women in western Pennsylvania.

Pulmonary Function

White and Froeb (1980) reported on 2,100 asymptomatic adults drawn from a population enrolled in a physical fitness program (Table 5). They reported statistically significant decreases in FEV_1 and maximum midexpiratory flow rate (MMEF) as a percent of predicted in nonsmokers exposed to tobacco smoke in the work environment for at least 20 years compared with nonsmoking workers not exposed. The magnitude of effect was comparable to that of actively smoking 1 to 10 cigarettes per day. However, the absolute magnitude of the difference in mean levels of function between the smoke-exposed group and the unexposed group was small: 160 mL (5.5 percent) for FEV_1 and 465 mL per second (13.5 percent) for MMEF. Carbon monoxide levels were measured in selected workplaces and ranged from 3.1 to 25.8 ppm. The study population was self-selected, and the exposure classification was crude and did not account for people who changed jobs. It is unclear how the ex-smokers in the population were handled in the analysis. Kentner and coworkers (1984) performed a cross-sectional investigation on 1,351 workers and found no influence of involuntary smoking on pulmonary function. In this study, involuntary smoking at home and at work was considered.

Comstock and colleagues (1981) examined 1,724 subjects drawn from two separate studies in Washington County, Maryland. Male and female nonsmokers married to smokers did not have a significantly increased risk of having an FEV_1 less than 80 percent of predicted or an FEV_1/FVC ratio less than 70 percent. Schilling and colleagues (1977) also did not find an effect of involuntary smoking in adults. Effects were not examined within strata defined by age in either of these studies.

TABLE 5.--Pulmonary function in adults exposed to involuntary smoking

Study	Subjects	Pulmonary function measured	Outcome	Comments
White and Froeb (1980)	2,100 adults, San Diego, California, United States	FVC, FEV_1, and MMF as percent predicted	Significant effect of office exposure to involuntary smoke	Potential selection bias; only current cigarette smoke exposure assessed treatment of ex-smokers unclear
Comstock et al. (1981)	1,724 adults, Washington County, Maryland, United States	FEV_1 as percent predicted	No effect of wives' smoking on husband's pulmonary function	Includes adults aged 20+ Cross-sectional study
Kauffmann et al. (1983)	7,818 adults, selected subgroups, seven cities, France	FEV_1, FVC, and MMEF	All measures significant effect in wives of smoking husbands; only MMEF significant in husbands of smoking wives	Not height adjusted; dose-response to amount of husbands' smoking for MMEF in wives; no effect below age 40 Cross-sectional study
Brunekreef et al. (1985)	173 adults, subgroups of larger study, the Netherlands	Peak flow, inspiratory vital capacity (IVC), FEV_1, and MMEF	Significant effect in wives of smoking husbands for peak flow FEV_1 cross-sectionally; no effect longitudinally	Small sample size
Kentner et al. (1984)	1,851 adult office workers, Germany	FVC, FEV_1	No effect of work exposure on pulmonary function	Cross-sectional study

Kauffmann and colleagues (1983) suggested that the effects of exposure from a spouse who smoked may be manifest only after many years of exposure. These investigators assessed the effects of marriage to a smoker in 7,818 adults drawn from several cities in France. Among 1,985 nonsmoking women aged 25 to 59, 58 percent of whom had husbands who smoked, the level of MMEF was significantly reduced in women married to smokers compared with women married to nonsmokers; this effect did not become apparent until age 40. The reduction was small, on average.

Recently, studying another population, Kauffmann and colleagues (1986) suggested that the FEV_1/FVC ratio may be a more sensitive test for detecting differences between exposed and nonexposed subjects, particularly in those with symptoms of wheezing; however, this suggestion has not been evaluated in other populations.

Brunekreef and coworkers (1985), from the Netherlands, reported on 173 nonsmoking women who were participants in a larger longitudinal study of pulmonary function. The women were classified by whether they were or were not exposed to tobacco smoke at study onset or at followup. Cross-sectionally, significant differences in pulmonary function were observed between smoke-exposed and nonexposed women. However, the rate of decline of lung function during the followup period was not affected by tobacco smoke exposure in the home. This study had a small number of subjects and inadequate statistical power to detect effects of exposure on rate of decline that were not extremely large.

Jones and colleagues (1983) selected women with either high or low FEVs from a population-based longitudinal study in Tecumseh, Michigan. Exposure to cigarette smoke at home from husbands who smoked was not significantly different in the two groups of women.

Nonsmoking men who participated in the Multiple Risk Factor Intervention Trial had significantly lower levels of pulmonary function if their wives smoked in comparison with similar men whose wives did not smoke (Svendsen et al. 1985).

The physiologic and clinical significance of the small changes in pulmonary function found in some studies of adults remains to be determined. The small magnitude of effect implies that a previously healthy individual would not develop chronic lung disease solely on the basis of involuntary tobacco smoke exposure in adult life. Whether particular characteristics increase susceptibility, such as childhood exposures or illnesses, atopy, reduced pulmonary function from whatever cause, and increased airways responsiveness, remains unknown. These small changes may also be markers of an irritant response, possibly transient, to the irritants known to be present in environmental tobacco smoke.

Bronchoconstriction

Normal Subjects

Only limited data have been published on the acute effects of inhalation of environmental tobacco smoke on pulmonary function in normal subjects (Table 6) and none on bronchial responsiveness. The available data have been obtained in exposure chambers under carefully monitored and controlled circumstances (Pimm et al. 1978; Shephard et al. 1979; Dahms et al. 1981).

Pimm and colleagues (1978) exposed nonsmoking adults to smoke in an exposure chamber. Relatively constant levels of carbon monoxide (approximately 24 ppm) were achieved in the chamber during involuntary smoking. Peak blood carboxyhemoglobin levels were always less than 1 percent in these subjects before smoke exposure, but were significantly greater after the study exposure. Lung volumes, flow volume curves, and heart rates were measured for all subjects. Measurements were made at rest and following exercise under control and smoke-exposure conditions. Flow at 25 percent of the vital capacity was reduced at rest in men and with exercise in women. Although statistically significant, the magnitude of the change was small: a 7 percent decrease in flow in men and 14 percent in women.

Shephard and coworkers (1979) utilized a similar cross-over design in a chamber of exactly the same size as that used by Pimm and associates. Their results were similar, with a small (3 to 4 percent) decrease in FVC, FEV_1, V_{max50}, and V_{max25}. They concluded that these changes were of the magnitude anticipated from exposure to the smoke of less than one-half of a cigarette in 2 hours (the exposure anticipated for an involuntary smoker).

Dahms and colleagues (1981) used a slightly larger chamber and an exposure with an estimated peak carbon monoxide level of approximately 20 parts per million. They found no change in FVC, FEV_1, or FEF_{25-75} in normal subjects after 1 hour of exposure.

The active smoker manifests acute responses to the inhalation of cigarette smoke; thus, high-dose involuntary exposure to tobacco smoke may plausibly induce similar responses in nonsmokers. The magnitude of these changes is quite small, even at moderate to high exposure levels, and it is unlikely that this change in airflow, per se, results in symptoms.

Asthmatics

Dahms and colleagues (1981) exposed 10 patients with bronchial asthma and 10 normal subjects to cigarette smoke in an environmental chamber. Pulmonary function was measured at 15-minute intervals for 1 hour after smoke exposure. Blood carboxyhemoglobin levels were measured before and after the l-hour exposure. The

TABLE 6.—Acute effects on pulmonary function of passive exposure to cigarette smoke; normal subjects

Study	Type of exposure	Magnitude of exposure	Effects	Comments
Pimm et al. (1978)	Chamber 14.6 m, furniture sparse, smoking machine in room	Peak [CO] ~ 24 ppm; particulates >4 mg/m^3	Men: 5% increase FVC, 11% increase RV, 4% decrease $\dot{V}_{max25}$ during exercise Women: 7% decrease $\dot{V}_{max25}$ after exercise; no effects on VC, TLC, FVC, FEV_1, $\dot{V}_{max50}$	Nonsmokers; average age, men 22.7, women 21.9; sham exposure as control
Shephard et al. (1979)	As above	Low exposure: peak [CO] ~ 20 ppm, particulates ~ mg/m^3; high exposure: [CO] ~ 31 ppm	Low exposure: 3% decrease FEV_1, 4% decrease $\dot{V}_{max50}$, 5% decrease $\dot{V}_{max25}$ with exercise; no increased effect with high exposure	Nonsmokers: average age, men 23, women 25; sham exposure as control; subject estimated inhalation ~ 1/2 cigarette/2 hours
Dahms et al. (1981)	Chamber 30 m, climate controlled	Room levels not measured; estimated at peak [CO] ~ 20 ppm	0.9% increase in FVC, 5.2% increase in FEV_1, 2.2% increase in FEF at 1 hour	10 nonsmokers; age range 24–53 years; not blinded; no sham exposure

carboxyhemoglobin levels in subjects with asthma increased from 0.82 to 1.20 percent. In normal subjects the increase was from 0.62 to 1.05 percent. The increases in carboxyhemoglobin in the two study groups were not significantly different. Asthmatic subjects had a decrease in forced vital capacity (FVC), FEV_1, and MMEF to a level significantly different from their preexposure values. The decreases in asthmatic subjects were present at 15 minutes, but worsened over the course of the hour to approximately 75 percent of the preexposure values. Normal subjects had no change in pulmonary function with this level of exposure. In this study, subjects were not blinded as to the exposure and were selected because of complaints about smoke sensitivity.

Shephard and colleagues (1979), in a very similar experiment, subjected 14 asthmatics to a 2-hour cigarette smoke exposure in a closed room (14.6 m^3). The carbon monoxide levels (24 ppm) were similar to those predicted in the study of Dahms and coworkers (1981). Blood carboxyhemoglobin levels were not measured. Subjects were randomized and blinded to sham (no smoke) and smoke exposure and tested on two separate occasions. Data were expressed as the percentage change from the sham exposure. Significant changes in FVC and FEV_1 were not observed between the sham and the smoke exposure periods, although 5 of 12 subjects did report wheezing or tightness in the chest on the day of smoke exposure.

Wiedemann and associates (1986) examined nonspecific bronchial responsiveness to methacholine in 9 asthmatic subjects and 14 controls and the effect of acute involuntary smoking on nonspecific bronchial responsiveness. At the time of the study, all asthmatics were stable with normal or near normal pulmonary function. The subjects underwent baseline pulmonary function and methacholine challenge testing. On a separate day they were exposed to cigarette smoke for 1 hour at 40 to 50 ppm of carbon monoxide and underwent pulmonary function and methacholine challenge testing. Pulmonary function was not influenced by exposure. Nonspecific bronchial responsiveness decreased significantly, rather than increasing, as would be anticipated following an irritant exposure.

Acute exposure in a chamber may not adequately represent exposure in the general environment. Biases in observation and the in selection of subjects and the subjects' own expectations may account for the widely divergent results. Studies of large numbers of individuals with measurement of the relevant physiologic and exposure parameters will be necessary to adequately address the effects of environmental tobacco smoke exposure on asthmatics.

Ear, Nose, and Throat

There are no studies of chronic ear, nose, and throat symptoms in adults with involuntary smoking exposure.

Lung Cancer

This section reviews the epidemiological evidence on involuntary smoking and lung cancer in nonsmokers, which has been derived from retrospective and prospective epidemiological studies. First, common methodological issues that apply to all these studies are considered. Second, for each type of study design, individual studies are reviewed for their methodological approach (Tables 7 and 8), findings associated with tobacco smoke exposure (Table 9, Figure 5), and strengths and limitations. Third, the lung cancer risk associated with involuntary smoking is examined as a low-dose exposure to cigarette smoke by combining the dose-response relationships for active smoking with the exposure data for involuntary smoking to predict the expected lung cancer risk due to involuntary smoking. This expected risk is then compared with the actual risks observed in studies of involuntary smoking. Finally, the existing epidemiological evidence is summarized and the plausibility of the association between lung cancer and involuntary smoking is evaluated on the basis of our current knowledge.

Observed Risk

General Methodological Issues

For both retrospective and prospective studies, the common methodologic concerns are disease misclassification and misclassification of the subject's personal smoking status or exposure to ETS. Disease misclassification, for example, refers to the incorrect classification of the lung as the primary site of a cancer that originated elsewhere. Disease misclassification is of greatest concern in studies in which the diagnosis of lung cancer was not histologically confirmed. Such misclassification tends to be random and to bias relative risk estimates toward unity (Copeland et al. 1977). Patients with lung cancer, or any disease associated with cigarette smoke exposure, may report exposure to ETS more frequently than controls because of bias in recall.

Misclassification of the subject's personal smoking status may occur in both retrospective and prospective studies; this misclassification refers to incorrectly classifying a subject as a nonsmoker when the subject is actually an ex-smoker or a current smoker, or to incorrectly classifying the subject as a smoker when the subject is a nonsmoker. Biochemical markers such as cotinine and nicotine, which can be used to detect unadmitted active smokers, are sensitive only to a recent exposure to tobacco smoke; thus, they are not particularly useful for identifying ex-smokers who deny their past smoking histories. Misclassification of smokers or ex-smokers as nonsmokers may produce the appearance of an involuntary smoking effect when, in fact, the true relationship is with active smoking.

TABLE 7.--Description of prospective studies

Factor	Studies		
	Hirayama	Garfinkel	Gillis
Source of subjects	Census population, 29 health districts, Japan	Volunteers, 25 States, United States	Health survey participants, two urban areas, Scotland
Nonsmoker population size (sex)	91,450 (F)	176,739 (F)	827 (M) 1,917 (F)
Age range	≥ 40	35-84	45-64
Years of enrollment	1966	1959-1960	1972-1976
Last year of followup	1981, 1983	1972	1982
Method of follow-up	Record linkage between risk factor records and death certificates	Monitored by ACS volunteers, death certificates from local/State health departments	Record linkage with Registrar General files
Verification of diagnosis	None	Verified method of diagnosis and histology for first 6 years' followup	Local cancer registry
Method and type of information obtained	Interview (?): smoking and drinking habits, dietary history, occupation, other health-related variables	Self-administered questionnaire: education, residence, occupational exposure, smoking and medical history	In-person interview: smoking habits, symptoms of respiratory and cardiovascular diseases
Index of passive Smoking	Husband's smoking at entry: nonsmoker, ex-smoker, current smoker (cig/day)	Husband's smoking at entry: nonsmoker, current smoker, and cig/day; ex-smokers excluded	Spouse's smoking at entry: current or never smoker; ex-smokers excluded (quit ≥ 5 years before entry)
Number of lung cancer deaths in nonsmokers	200 (F)	153 (F)	6 (M), 8 (F)

SOURCE: Hirayama (1981a, 1983,1984a, b), Garfinkel (1981), Gillis et al. (1984).

Misclassification of involuntary smoking exposure refers to the incorrect categorization of exposed subjects as nonexposed and of nonexposed subjects as exposed. Most studies of lung cancer to date have used the number of cigarettes smoked by spouses as a measure of exposure to involuntary smoking, and thus have disregarded duration of exposure, exposure from other sources, and factors that influence exposure, such as proximity to the smokers or size and ventilation of the room where the exposure occurred. Moreover, all

TABLE 8.--Description of case-control studies

Study	Country	Case	Control	Respondent and type of interview	Confirmed history		Index of passive smoke: habits of spouses and others
		Source and type	Source and type		Pathological/ cytological	Adenocarcinoma	
Trichopoulos et al. (1981, 1983)	Greece	Chest and cancer hospitals; 77 NS (F)	Orthopedic hospital; 225 NS; not matched	Self; not blinded	65%	Presumed none	Current and former spouses (amount. yr); no other
Correa et al. (1983)	New Orleans, United States	Hospitals; 30 NS (8 M, 22 F)	Same hospitals, non-tobacco-related diseases; 313 NS (180 M, 133 F); matched for age, sex, race, hospital	Self, and proxy (case, 23%; control, 11%); blinded	97%	54% among women	Current spouse (type, amount, yr); parents
Ghan and Fung (1982)	Hong Kong	Four hospitals: 84 NS (F)	Orthopedic, same hospitals; 139 NS; not matched	Self; not blinded	82%	45%	Not spouse specifically; one question: at home and at work
Koo et al. (1983,1984)	Hong Kong	Eight hospitals, 88 NS (F)	Population; 137 NS; matched for age, race, sex, socioeconomic status, residence district	Self; not blinded	97%	59%	Current and former spouses (amount, yrs hrs); parents other cohabitants coworkers (amount, yrs. hrs)
Kabat and Wynder (1984)	United States	Most from one NY hospital; 134 NS; passive smoking data on only 78 NS (25 M, 53 F)	Same hospital (?); non-tobacco-related disease; 78 NS (25 M, 53 F); matched for age, sex, race, hospital, date of interview, nonsmoking status	Self; not blinded	100%	54% M 74% F of 134 NS	Current spouse (present or past smoking habits); current exposure at home and work

TABLE 8.--Continued

Study	Country	Case	Control	Respondent and type of interview	Confirmed histology		Index of passive smoke: habits of spouses and others
		Source and type	Source and type		Pathological/ cytological	Adenocarcinoma	
Wu et al. (1985)	Los Angeles, United States	Population-based registry; 29 NS (F)	Population; 62 NS; matched for age, race, sex, neighborhood	Self; not blinded	100%	100%	Current and former spouses (amount, yrs); parents, cohabitants (amount, yrs). coworkers (hr/day, yrs)
Garfinkel et al. (1965)	New Jersey, Ohio, United States	Four hospitals, 134 NS (F)	Same hospitals, colorectal cancer patients; 402 NS; matched for age, hospital, nonsmoking status	Self (case, 12%; control, ?) and proxy; blinded	100%	65%	Current spouse or cohabitant (total and at home: amount, yrs); other exposure, average hrs/day (at home, work. other) 5 and 25 yrs before diagnosis; childhood exposure

TABLE 8.—Continued

Study	Country	Case: Source and type	Control: Source and type	Respondent and type of interview	Confirmed histology: Pathological/ cytological	Confirmed histology: Adenocarcinoma	Index of passive smoke: habits of spouses and others
Lee et al. (1986)	United Kingdom	Hospital-based; 47 NS (15 M, 32 F)	Same hospitals; 96 NS (30 M, 66 F); matched for age, sex, marital status, hospital	Self, hospital inpatient interview; Spouse, followup interview; not specified	?	?	Current spouse (smoking habit during admission yr and maximum during marriage); other exposure at home, at work, during travel and leisure
Akiba et al. (1986)	Japan	Hiroshima and Nagasaki bomb survivors; 103 NS (19 M, 84 F)	Same cohort, noncancer or chronic respiratory disease; 380 NS (110 M, 270 F); matched for age, sex, city of residence, vital status, yr of death	Self (case, 10%; control, 12%) and proxy; not blinded	57%	?	Current spouse (amount, age start, age stop, yrs cohabited); parents
Pershagen et al. (in press)	Sweden	National census of Sweden and Swedish Twin Registry; 67 NS (F)	Two controls from each source; 347 NS; matched for year of birth, vital status at followup end for twin registry control	Self, and proxy (case, almost all; control, ≥65%); not applicable, mailed questionnaire	99%	57%	Spouse lived with longest (amount, yrs); parents

TABLE 9.--Results from selected prospective and case-control studies; lung cancer risk associated with spouses' smoking

Study	Spouses' smoking				
	Nonsmoker	Ex-smoker	1-14/day	15-19/day	20+/day
Hirayama (1984a)	1.0	1.4 (0.9, 2.2) [1]	1.4 (1.0, 2.0)	1.6 (1.0, 2.4)	1.9 (1.3, 2.71)
	Nonsmoker	<20/day		20+/day	
Garfinkel (1981)	1.0	1.3 (0.9, 1.9)		1.1 (0.8, 1.6)	
		Not exposed		Exposed	
Gillis et al. (1984)	Men	1.0		4.3	
	Women	1.0		1.0	
	Nonsmoker	Ex-smoker	1-20/day	21+/day	
Trichopoulos et al. (1983)	1.0	1.9 (0.9, 4.1)	1.9 (1.0, 3.7)	2.5 (1.7, 3.8)	
	Nonsmoker	1-40 pack-yr		>41 pack-yr	
Correa et al. (1983)	1.0	1.5 (0.6, 3.8)		3.1 (1.1, 8.5)	
	No	Yes			
Chan and Fung (1982)	1.0	0.8 (0.5, 3.1)			
	Nonsmoker	≤ 35,000 hrs[2]		≥ 35,000 hrs	
Koo et al. (1984)		1.3 (0.8, 2.4)		1.0 (0.2, 2.7)	
	No	Yes			
Kabat and Wynder (1984)	1.0	0.9 (0.3, 2.1)			
	Nonsmoker	l-20 yrs		21+ yrs	
Wu et al. (1985)	1.0	1.4 (0.4, 4.9)		1.2 (0.4, 3.7)	
	Nonsmoker	Cigar/pipe	<10/day	10-19/ day	≥ 20/day
Garfinkel et al. (1985)	1.0	1.2 (0.8, 1.7)	1.2 (0.8, 1.6)	1.1 (0.8, 1.5)	2.1 (1.1, 4.0)
	No	Yes			
Lee et al. (1986)	1.0	1.1 (0.5, 2.4)			
	Nonsmoker	l-19/day	20-29/day	30+/day	
Akiba et al. (1986)	1.0	1.3 (0.7, 2.3)	1.5 (0.8, 2.8)	2.1 (0.7, 2.5)	
	Nonsmoker	Low[3]		High[4]	
Pershagen et al. (in press)	1.0	1.0 (0.6, 1.8)		3.2 (1.0, 9.5)	

[1]Numbers in parentheses are the 95 percent confidence limits.

[2]Total exposure from spouses. cohabitants, coworkers.

[3]Husband smoked ≤ 15 cigarettes/day or 1 pack (50 g) of pipe tobacco/week or any amount during < 30 years of marriage.

[4]Hushand smoking > 15 cigarettes/day or 1 pack of pipe tobacco/week during ≥ 30 years of marriage.

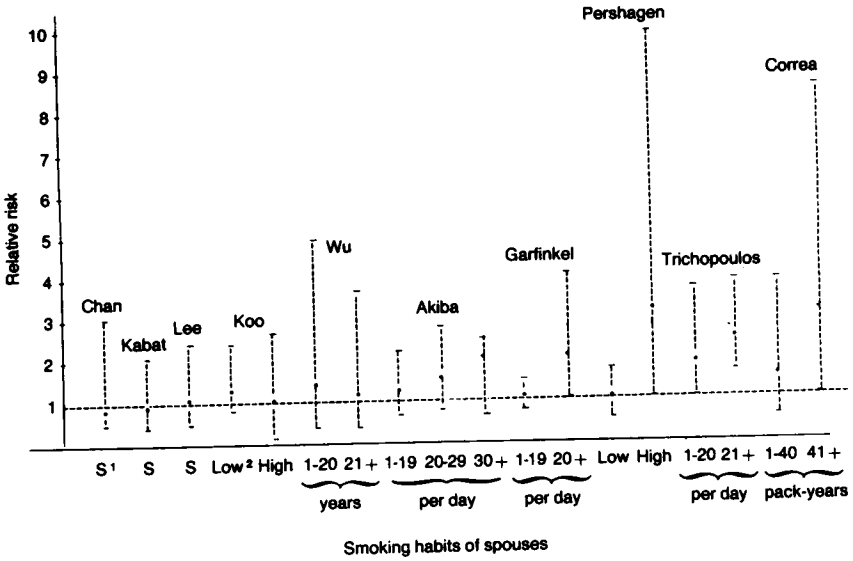

FIGURE 5.—Relative risks and 95 percent confidence intervals in case–control studies of passive smoking and lung cancer

[1] S=smoker.

[2] Low and high exposure levels are described in Table 9.

SOURCE: Chan and Fung (1982); Kabat and Wynder (1984); Lee et al. (1986); Koo et al. (1984); Wu et al. (1985); Akiba et al. (1986); Garfinkel et al. (1985); Pershagen et al. (in press); Trichopoulos et al. (1983); Correa et al. (1983).

of the published studies have based involuntary smoking exposure measures on questionnaires without validation of these data with biochemical markers or environmentally measured concentrations of tobacco smoke constituents. Misclassification of involuntary smoking exposure is likely to be random and to bias the effect measures toward the null (Copeland et al. 1977).

Misclassification of exposure to environmental tobacco smoke is inherent in epidemiological studies of involuntary smoking. Tobacco smoking has not been restricted in most indoor environments until recently, and exposure has been almost inevitable in the home, the workplace, or other locations. Studies with the biological markers nicotine and cotinine confirm that tobacco smoke exposure is widespread; detectable levels of these markers are found even in people without reported recent exposure. Thus, the exposure variables employed in epidemiological studies do not separate nonexposed subjects from exposed subjects; instead, they discriminate more exposed groups from less exposed groups. As a result, the

epidemiological approach is conservative in estimating the effects of involuntary smoking. A truly nonexposed but otherwise equivalent comparison population has not been identified. The extent of the resulting bias cannot be readily estimated and probably varies with the exposure under consideration, which may be one reason for the variability in risk estimates obtained by different studies.

Information bias is an added concern in case-control studies, since neither interviewer nor respondent bias can be ruled out. It is not feasible to blind interviewers to the case or control status of respondents because of the usually obvious manifestations of lung cancer and because of the setting in which some of the interviews are conducted. Moreover, blinding of interviewers and respondents to the study hypothesis is difficult because the majority of questions are concerned with exposure to tobacco smoke. The direction of the information bias may be dependent on the type of respondent. Self-respondents may be more apt to interpret their disease as related to exposure to tobacco smoke and thus overreport the exposure. However, the direction of the information bias is less clear when interviews are conducted with surrogate respondents. The ability of a surrogate to provide accurate information may depend on the relationship of the surrogate respondent to the subject, whether the surrogate lived with the subject during the time frame of the questions asked, the degree of detail requested, and the amount of time elapsed since the event in question (Gordis 1982; Pickle et al. 1983; Lerchen and Samet 1986). Surrogate respondents may minimize the reporting of their own smoking because of guilt, or may overreport about involuntary smoking exposure in an attempt to explain their relative's illness. Thus, depending on the direction of the information bias, it may dilute or strengthen the effect being measured (Sackett 1979). In general, however, the information on smoking status and on amount smoked provided by surrogates has been found to be fairly comparable to that provided by the individuals themselves (Blot and McLaughlin 1985).

Finally, participants and nonparticipants in case-control studies may be inherently different with respect to their exposure to involuntary smoking because their awareness of the hypothesis under study may motivate the decision to participate. However, participants in case-control studies are generally not informed of the hypothesis under study.

Spousal Exposure: Prospective Studies

The Japanese Cohort Study

Hirayama (1981a, 1983, 1984a) has presented data from a large cohort study that included 91,540 nonsmoking married women who were residents of 29 health districts in Japan. Subjects were 40 years

of age or older at enrollment in 1965; information was collected on smoking and drinking habits, diet (e.g., green-yellow vegetables, meat), occupation, and other health-related variables.

The initial report on involuntary smoking was based on 14 years of followup (1966-1979). The husbands' smoking histories were available for 174 of 240 lung cancer cases identified among the nonsmoking married women (Hirayama 1981a); this number increased to 200 with 2 additional years of followup (Hirayama 1983, 1984a). Results pertaining to the association of spouses' lung cancer risk with the husbands' smoking were essentially identical in the first and second reports.

On the basis of the smoking habits of the husbands at entry, the 200 nonsmoking women were classified as married to a nonsmoker, an ex-smoker, or a current smoker. The lung cancer mortality ratios standardized by husband's age were 1.00, 1.36, 1.42, 1.58, and 1.91 for women whose husbands were nonsmokers, ex-smokers, and daily smokers of 1 to 14, 15 to 19, and 20 or more cigarettes, respectively (one-sided p for trend, 0.002). Similarly significant dose-response trends were observed when the mortality ratios were standardized by age of the wives, by occupation of the husbands (agricultural, industrial, other), by age and occupation of the husbands, and by the time period of observation (1966-1977 versus 1978-1981). The risk of lung cancer among nonsmoking wives of smokers was reduced to 0.7 (two-sided p=0.05) if they ate green-yellow vegetables daily compared with 1.0 if they ate such vegetables less often than daily (Hirayama 1984b). No other characteristic of the wives (e.g., drinking habits, parity, occupation, nonvegetable dietary items) or of the husbands (e.g., drinking habits) was significantly predictive of lung cancer risk.

Nonsmoking men whose wives were smokers also showed an elevated lung cancer risk. On the basis of 67 lung cancers in nonsmoking married men, the lung cancer mortality ratios were 1.00, 2.14, and 2.31 if their wives had never smoked or had smoked 1 to 19 cigarettes or 20 or more cigarettes per day, respectively (one-sided p for trend, 0.023) (Hirayama 1984b).

This study has been critically discussed in correspondence since its initial publication. Because a detailed breakdown of the at-risk population was not presented in the initial report, the lung cancer mortality rate was thought by some to be higher in the unmarried nonsmoking women than in the nonsmoking women married to smokers (Rutsch 1981; Grundmann et al. 1981). This impression was clarified by the researcher (Hirayama 1981b,c,d) and shown to be the result of incorrect interpretation of data in the original paper. Other potential problems cited were sampling bias in the study cohort, misclassification in the diagnosis of lung cancer, misclassification of the nonsmoking status of wives, misclassification of involuntary

smoking exposure, failure to control for potential confounders, and inadequate statistical treatment of data. Each of these points of criticism is discussed below.

MacDonald (1981a,b) questioned the representativeness of the 29 health districts selected in the study cohort and suggested that industrial pollution, such as asbestos exposure from shipbuilding industries specific to the selected health districts, may have biased the results. However, the levels of exposure to this factor would have to coincide with the husbands' smoking level to explain the effect observed. Such an association seems unlikely. If the cohort were not representative, the generalizibility but not the validity of the findings would be challenged (Criqui 1979).

The accuracy of the diagnosis of primary lung cancer on the basis of death certificates and the adequacy of the data without information on the histology of the tumor were questioned (Grundmann et al. 1981; MacDonald 1981a). From a sample of 23 cases, Hirayama (1981b) reported that the distribution by histology of lung cancer in nonsmoking women whose husbands smoked was similar to that in women who smoked. Failure to discriminate in some cases between primary and metatastic lesions to the lung may be a potential problem with disease diagnosis. Although Hirayama was unable to assess the accuracy of the diagnosis listed on the death certificate, there is no reason to believe that error in recording the causes of death of wives was influenced by the smoking habits of their husbands, and any misclassification is likely to be random. Inclusion of nonlung cancer cases would tend to bias the risk ratio toward unity or no effect (Barron 1977; Greenland 1980).

The relatively high risks observed for nonsmokers whose husbands smoked led to speculation that Japanese women may report themselves as nonsmokers when they actually smoke (Lehnert 1984). However, some assurance of the reliability of the smoking data provided by the Japanese women comes from an investigation in Hiroshima and Nagasaki (Akiba et al. 1986) that found strong concordance between smoking status reported by the women themselves and that reported by their next of kin.

Classifying nonsmoking women solely on the basis of the smoking habits of their current husbands probably does not quantify their exposure with precision because it accounts for only one of the many possible sources of tobacco smoke exposure. Moreover, using the number of cigarettes smoked per day by the husbands as a measure of exposure dose assumes that the husbands' increasing daily cigarette consumption is directly related to an increasing ETS exposure of the wives (Kornegay and Kastenbaum 1981; Lee 1982b).

The analyses were further criticized for not accounting for potential confounding factors such as socioeconomic status (SES) and exposure to indoor air pollutants (e.g., from heating and cooking

sources) (Sterling 1981). However, Hirayama showed a fairly consistent relationship between involuntary smoking exposure and lung cancer across SES categories. The role of indoor air pollutants could not be addressed directly in the study, but data from one health district in the study indicated no association between heating or cooking practices and the smoking habits of the husbands (Hirayama 1981b).

The researcher's failure to specifically describe the methods for age standardization in the initial report led to speculation that the statistical methods used were incorrect (Kornegay and Kastenbaum 1981; Mantel 1981; Tsokos 1981; Lee 1981); however, the calculations were later confirmed (Harris and DuMouchel 1981; Hammond and Selikoff 1981). The choice of stratification variables used for age standardization was also criticized because the husbands' ages instead of the wives' ages and 10-year age groups instead of narrower ones were used (Tsokos 1981; MacDonald 1981b). Later publications confirmed that similar results were obtained regardless of the method of standardization (Hirayama 1984a).

The American Cancer Society Cohort Study

A second prospective study (Garfinkel 1981) that examined the effects of involuntary smoking was the American Cancer Society (ACS) study of about 1 million people living in 25 States. A self-administered questionnaire on education, residence, occupational exposure, and smoking and medical history was completed by the study subjects upon enrollment.

This report on involuntary smoking was based on 12 years of followup (1960-1972) and included 176,739 nonsmoking married women whose husbands' smoking habits were available and whose husbands were never smokers or current smokers. In the total cohort of nonsmoking women, 564 lung cancer deaths occurred, and data on the husbands' smoking habits were available for 153 (27.1 percent). Wives of ex-smokers and of cigar or pipe smokers were excluded from the analysis.

A small, statistically nonsignificant increased risk for lung cancer was found for nonsmokers married to smokers. The mortality ratios for lung cancer in nonsmoking women were 1.0, 1.27, and 1.10 when the husbands were nonsmokers, daily smokers of fewer than 20 cigarettes, and daily smokers of 20 or more cigarettes, respectively. The results were essentially unchanged after accounting for the potential confounding effects of age, race, education, residence, and husband's occupational exposure.

The ACS study, like the Japanese study, was not designed to study the long-term effects of involuntary smoking. However, the ACS study does provide an estimate of the extent of misclassification of lung cancer. On the basis of medical record verification, the death

certificate diagnosis of lung cancer in nonsmoking women was incorrect for 12 percent of the cases. Although confirmation of diagnosis was sought only for the first 6 years of followup, the available data suggest that some misclassification of lung cancer occurred. To the extent that passive smoking is related to lung cancer in nonsmokers, inclusion of nonlung cancers would tend to dilute a true effect.

A limitation of the ACS study is the nonavailability of smoking information on the husbands of a large proportion of the nonsmoking women who died of lung cancer. Because smoking habits are correlated with various social characteristics, this large loss of information may have created a bias in this study. The researcher stated that an index of tobacco smoke exposure based only on smoking habits of current husbands may be particularly inadequate for the United States, with its high rate of divorce and substantial proportion of women working outside the home. This speculation is supported by data from a group of 37,881 nonsmokers and ex-smokers who were members of a health plan in California. Friedman and colleagues (1983) stated that 47 percent of the nonsmoking women and 39 percent of the nonsmoking men married to smokers reported no exposure at home. Moreover, being married to a nonsmoker did not assure the absence of exposure to tobacco smoke, since 40 percent of the nonsmoking women and 49 percent of the nonsmoking men married to nonsmokers reported some exposure to tobacco smoke during the week. Thus, random misclassification could have biased the results toward unity and led to an underestimate of the effect of passive smoking.

The Scottish Study

Gillis and colleagues (1984) conducted a prospective cohort study of 16,171 Scottish men and women, aged 45 to 64 years, from two urban areas, who attended a multiphasic health screening clinic between 1972 and 1976. A questionnaire on smoking habits and symptoms of respiratory and cardiovascular diseases was completed at entry into the study.

The preliminary analysis of involuntary smoking, representing 6 to 10 years of followup, was based on the 2,744 nonsmokers among the 8,128 subjects who lived as couples and could be paired according to smoking habits. Subjects who lived alone or whose partner did not participate and ex-smokers who had stopped smoking for 5 years or more were excluded. The nonsmokers were classified as nonsmokers not exposed to environmental tobacco smoke or as nonsmokers exposed to environmental tobacco smoke, according to the smoking habits of their spouses.

A higher age-standardized lung cancer mortality rate was reported for nonsmoking men exposed to tobacco smoke (13 per 10,000) than

for nonsmoking men not exposed (4 per 10,000); however, no statistical tests were conducted because of the small number of cancers. Lung cancer rates were similar for nonsmoking women regardless of the status of their exposure to tobacco smoke (4 per 10,000). The extremely small number of observed lung cancer deaths (6 men, 8 women) limit the interpretation of the study's findings.

Spousal Exposure: Case-Control Studies

Table 8 summarizes the case-control studies that have examined the relationship between involuntary smoking exposure and lung cancer.

The Greek Study

Trichopoulos and colleagues (1981, 1983; Trichopoulos 1984) examined the effect of involuntary smoking on lung cancer risk in a case-control study of 51 Caucasian female lung cancer patients (excluding adenocarcinoma and terminal bronchiolar carcinomas) from three chest hospitals and 163 female controls from an orthopedic hospital in Athens, Greece. All subjects were interviewed in person by one physician who questioned them regarding their personal smoking habits and those of their current and former husbands. Thirty-five percent of the cases were diagnosed only on the basis of clinical or radiologic information; the remainder were cytologically (37 percent) or histologically (28 percent) confirmed.

Nonsmoking women were classified by the smoking habits of their current or former husbands. Husbands were nonsmokers if they had never smoked or had stopped smoking more than 20 years previously, ex-smokers if they stopped 5 to 20 years previously, and current smokers if they were smoking or had stopped less than 5 years before the interview. Being never married, widowed, or divorced was equated as being married to a nonsmoker or an ex-smoker, depending on the length of time in the category.

The initial report was based on 40 nonsmoking cases and 149 nonsmoking controls. The odds ratios (ORs) for women married to nonsmokers, ex-smokers, current smokers of 1 to 20 cigarettes per day, and current smokers of 21 or more cigarettes per day were 1.0, 1.9, 2.4, and 3.4, respectively (two-sided p for trend, < 0.02). In a later report on 77 nonsmoking cases and 225 nonsmoking controls, the ORs were somewhat lower: 1.0, 1.9, 1.9, and 2.5, respectively (Trichopoulos et al. 1983; Trichopoulos 1984).

The findings of this study were questioned because the diagnosis of cancer was not pathologically confirmed for 35 percent of the cases (Hammond and Selikoff 1981; Lee 1982b). The inclusion of cases that were not lung cancers would tend to dilute the results toward the null because they may not be related to involuntary smoking.

Terminal bronchial (alveolar) carcinoma and adenocarcinoma of the lung were excluded from the pathologically confirmed group; this exclusion may have been premature (Hammond and Selikoff 1981; Kabat and Wynder 1984), as the causal association between personal smoking and adenocarcinoma of the lung is well established (IARC 1986). Because the controls were selected from a different hospital than were the cases, selection bias cannot be ruled out. Interviewer bias is also possible, since all subjects were interviewed by a single physician who knew the case or control status of each subject, and also knew the hypothesis under investigation.

The index of exposure to tobacco smoke used in this study included the smoking habits of former and current husbands. Since the definition of ex-smokers excluded those who had stopped smoking recently (within the last 5 years), it was unanticipated that the risks observed for women whose husbands were ex-smokers (i.e., quit 5 to 20 years previously) were as high as for those whose husbands were current smokers. Additional information on the smoking habits of these ex-smokers would be valuable.

The Louisiana Study

The case-control study by Correa and colleagues (1983) was based on 1,338 primary lung cancer cases, of which 97 percent were pathologically confirmed. Controls (N = 1,393) were matched to cases by race, sex, and age (±5 years) and were patients at the same hospitals as cases but without a diagnosis related to tobacco smoking.

Standardized interviews were conducted with the subjects (76 percent of cases, 89 percent of controls) or their next of kin. Questions on occupation, residency, personal smoking and drinking habits, and smoking habits (including type of tobacco smoked and amount and duration of smoking) of the current spouse and parents were asked.

Thirty nonsmoking ever-married lung cancer (excluding bronchioalveolar cell) patients (8 men, 22 women) and 313 ever-married nonsmoking controls (180 men, 133 women) were classified according to their spouse's total lifetime pack-years and current daily amount smoked at the time of interview. After adjusting for sex, ORs of 1.00, 1.48, and 3.11 were observed when spouses had smoked none, 1 to 40 pack-years, and 41 or more pack-years, respectively (two-sided $p < 0.05$). The results based on current daily number of cigarettes smoked by spouses were similar.

The study is limited by the small number of nonsmoking cases, but the consistency of the results for men and women strengthens the findings. Misclassification of involuntary smoking is possible because only smoking habits of the current husband were assessed, ignoring the effect of divorce, remarriage, and exposure from coworkers. Exposure from parents during childhood was determined, but case

numbers were too small for a meaningful analysis of this factor among nonsmokers.

The Hong Kong Studies

The high rates of lung cancer, particularly adenocarcinoma of the lung, among women of Chinese descent in Hong Kong are unexpected in the face of their low rates of tobacco smoking. The role of involuntary smoking was investigated in two studies conducted in Hong Kong (Chan et al. 1979; Chan and Fung 1982; Koo et al. 1983, 1984).

Chan and colleagues (1979) examined the role of involuntary smoking among 84 female lung cancer patients and 139 orthopedic control patients, none of whom had ever smoked. Of the 84 nonsmoking cases, 69 (82 percent) were pathologically confirmed, and 38 of these 69 cases were adenocarcinoma of the lung. The controls were from the same hospitals as the cases, but were not individually matched to the cases on any characteristics.

Cases and controls were questioned regarding their residence, education, occupation, cooking practices, and personal smoking habit. One question on exposure to others' tobacco smoke was included: "Are you exposed to the tobacco smoke of others at home or at work?" The researchers reported that the controls lived with smoking husbands more frequently (47.5 percent) than the cases (40.5 percent) (OR 0.77), but did not explain how this question was used to classify the habits of the spouse alone. The method used to classify currently unmarried respondents (i.e., never married, widowed, divorced) with regard to exposure to their spouses' smoking was not described, and it is not known if the nonsmoking cases and controls were comparable in terms of current marital and employment status. Thus, insufficient information on the measure used to assess ETS exposure, and on the comparability of the nonsmoking cases and controls, limits interpretation of this study's results.

The study by Koo and colleagues (1983, 1984) involved 200 Chinese female lung cancer patients who were identified from eight hospitals in Hong Kong; almost all cases were pathologically confirmed (97 percent). Among these women, 88 had never smoked, of whom 52 (59 percent) had adenocarcinomas of the lung. An equal number of "healthy" population controls, individually matched to cases by age (±5 years), socioeconomic status, and district of residence, were interviewed. Among the controls, 137 had never smoked.

Using a semistructured questionnaire, taped interviews were obtained and information on residence, occupation, family and medical history, personal smoking habits, and smoking habits of all cohabitants and coworkers was elicited. ETS exposure was quantified in hours and years according to who (i.e., husband, parents, in-laws, children, others) smoked in the subject's presence and where

(i.e., at home, at work) the exposure occurred. The analysis was based on a cumulative smoke exposure index (in total hours and total years) specific to place of exposure.

The investigators concluded that there was no association between involuntary smoking and lung cancer in nonsmoking Chinese women, regardless of the index of smoke exposure used. A small, but statistically nonsignificant, increased risk (RR 1.24) was associated with any exposure to tobacco smoke. There were no significant differences between the cases and the controls in total hours or total years of exposure. The results remained unchanged when exposure hours were categorized into three levels of exposure. Odds ratios of 1.00, 1.28, and 1.02 were associated with no, low ($\leq$ 35,000 hours), and high (> 35,000 hours) exposure levels, respectively. There was no apparent trend of lung cancer risk with the age when exposure to tobacco smoke began. The ORs for never exposed and first exposed at ages 0 to 19, 20 to 39, and 40 or older were 1.00, 0.96, 1.53, and 0.91, respectively (Koo et al. 1984). Analysis by cell type suggested that the effects of involuntary smoking may be more pronounced for Kreyberg I tumors (squamous, small-cell, and large-cell carcinomas) (OR 1.47, 95 percent C.I. 0.64, 3.36) than for adenocarcinoma (OR 1.11, 95 percent C.I. 0.49, 2.50) (Koo et al. 1985), but these numbers were small.

The design of this study addressed the criticisms of other studies that an index of involuntary smoking exposure based only on spouses' smoking habits is inadequate, and broadened the exposure assessment to include all locations of tobacco smoke exposure. However, the cumulative exposure index created in this study may have limited validity. Unlike personal smoking, where there is essentially one source (personal smoking), one dose (usual or maximum amount smoked), and one duration of exposure (age at start and age at stop), ETS exposure derives from diverse sources at different doses and durations of exposure. The accuracy of the information on exposure to ETS will depend on the amount of detail requested, the age of the respondent, the temporal course of the exposure, and the source of the exposure. Weighing each type of exposure equally in a cumulative index (in total hours) may be incorrect because it assumes that all sources of exposure should be quantified in the same way and that each source of tobacco smoke contributes equally, disregarding intimacy of contact and proximity to smokers and conditions of exposure (e.g., room size, ventilatory factors). Thus, random misclassification of the exposure variable by inclusion of data from less relevant exposures than spousal smoking may obscure an association of involuntary smoking exposure with lung cancer risk. In this study, interviewer and respondent bias should also be considered because a structured questionnaire was not used.

All of the cases of primary lung cancer in nonsmokers were selected (Kabat and Wynder 1984) from an ongoing case-control study of tobacco-related cancer conducted in five U.S. cities between 1971 and 1980 (Wynder and Stellman 1977). For each case, one control was individually matched by age (±5 years), sex, race, hospital, date of interview (±2 years), and nonsmoking status. Controls were selected from a large pool of hospitalized patients who were interviewed over the same time period as the cases and who had diseases not related to tobacco smoking. Information on demographic factors, residence, height and weight, drinking habits, previous diseases, and occupational exposure were obtained. Questions on tobacco smoke exposure at work, at home, and from current spouse were added in 1978 and revised in 1979. Information on ETS exposure was available for 25 of 37 nonsmoking male cases, 53 of 97 nonsmoking female cases, and their respective matched controls.

A higher percentage of female controls than of female cases reported exposure to ETS at home (32 percent), at work (59 percent), and from spouses (60 percent). The percentages of female cases who reported exposure at home, at work, and from spouses were 30, 49, and 54 percent, respectively. None of the case-control differences in women were statistically significant. Male cases reported more frequent exposure at work (OR 3.27, p=0.045) and at home (OR 1.261, but no difference in the smoking status of their spouses (OR 1.00).

The process for selecting the nonsmoking controls from the larger pool of controls in the ongoing study and for selecting the nonsmoking cases and controls who were questioned with regard to ETS exposure was not described adequately. It is not clear whether the 25 of 37 male and 53 of 97 female nonsmoking cases and controls who provided information on involuntary smoking were all interviewed during or after 1978 when the questions on involuntary smoking were introduced. The proportion seemed high, since it represented 68 percent of male and 55 percent of female nonsmoking cases interviewed during the 10 years of data collection. The study was not designed to specifically address the effect of involuntary smoking, and a variable subset of questions on involuntary smoking was asked, depending on when the subjects were interviewed. Misclassification of the exposure is possible because it is not clear whether the cases and controls answered the same set of questions and whether a comparable amount of information was obtained. The researchers acknowledged the limitations of this study and presented its results as preliminary findings.

The Los Angeles County Study

In the case-control study by Wu and colleagues (1985), 220 white female lung cancer patients (149 with adenocarcinoma and 71 with squamous cell carcinoma) and 220 population controls were individually matched on sex, race, age (±5 years), and neighborhood of residence. Cases were identified from the population-based tumor registry of Los Angeles County. All cases were histologically confirmed; the histological type was based on the pathology report from the hospital of diagnosis.

Using a structured questionnaire, cases and controls were directly interviewed by telephone and were asked about their own personal smoking habits and the smoking habits (amount and years of smoking) of current and former husbands, parents, and other household members during childhood and adult life. Exposure to tobacco smoke at work (in hours per day) was obtained for each job of at least 6 months' duration. Information on medical and reproductive history, heating and cooking sources, and dietary intake of vitamin A were obtained.

Of 149 patients with adenocarcinoma of the lung, 29 had never smoked, nor had 2 of 71 patients with squamous cell carcinoma. The analysis of involuntary smoking was based on the 29 nonsmokers among the adenocarcinoma cases and 62 nonsmokers among the controls.

A subject was classified as married to a smoker if any of her husbands had ever smoked. Similarly, a subject was considered exposed at work if she was exposed to tobacco smoke for at least 1 hour per day at any of her jobs. There were small, but nonsignificantly increased risks associated with ETS exposure from spouse or spouses (OR 1.2; 95 percent C.I. 0.2,1.7), and from coworkers (OR 1.3; 95 percent C.I. 0.5, 3.3). Increased risk was not associated with smoke exposure from either parent (OR 0.6; 95 percent C.I. 0.2, 1.7). Exposure to tobacco smoke from spouses and from coworkers was combined in an index representing smoke exposure during adult life. There was an increasing trend in risk with increasing years of exposure. The 0R.s were 1.0, 1.2, and 2.0 for 0,l to 30, and 31 or more years of involuntary smoking exposure during adult life, respectively, but the results were not statistically significant. Because the exposures may have occurred concurrently, the years of exposure represented units of exposure rather than calendar years of exposure.

This study is limited by the small number of nonsmoking cases and controls. Unlike the two case-control studies that excluded adenocarcinoma or bronchioalveolar cell carcinoma (Trichopoulos et al. 1981; Correa et al. 1983), cases in this analysis were of these cell types (17 adenocarcinoma, 12 bronchioalveolar); this case mix may explain the weak association observed.

The Four Hospitals Study

A case-control study by Garfinkel and colleagues (1985) included 134 nonsmoking female lung cancer cases selected from three hospitals in New Jersey and one in Ohio over an 11-year period, 1971-1981. Medical records served as the initial source of information on smoking status of the subject, and the nonsmoking status of each case and control was verified at interview. Three controls, colorectal cancer patients matched to cases by age (±5 years) and hospital, were interviewed for each case, giving a total of 402 controls. All diagnoses of cases and controls were pathologically confirmed. Interviewers, blinded to the diagnosis of the subjects and to the study hypothesis, administered a standard questionnaire to subjects or their next of kin. Information on the smoking habits of current spouse (total and amount smoked at home), tobacco smoke from other sources (in hours per day at home, at work, and in other settings), and exposure to tobacco smoke during childhood were obtained.

Subjects were classified according to the smoking habits of current husbands. Smoking habits of a cohabitant in the same household was used for single women or those who no longer lived with their spouses. Of the cases, 57 percent were classified according to the smoking habits of husbands; the corresponding percentage in controls was not provided. Nonsmoking women living with a smoker showed an elevated risk for lung cancer (OR 1.31). The ORs for lung cancer in nonsmoking women were 1.00, 1.15, 1.08, and 2.11 when the husbands were nonsmokers, daily smokers of less than 10, 10 to 19, and 20 or more cigarettes at home, respectively (one-sided p for trend, <0.025). Similarly, a significant positive linear trend (one sided $p < 0.025$) was shown when the husbands' total amount smoked was categorized into four levels. However, there was no apparent dose-related trend by years of exposure to the husbands' smoking (0, <20, 20-29, 30-39, 40+ years).

There was no apparent association between lung cancer and tobacco smoke exposure from other sources. Cases and controls did not differ in their reported exposure to tobacco smoke during childhood or in their average hours of exposure per day to other's tobacco smoke during the last 5 years and 25 years before diagnosis. The results remained unchanged when exposures at home, at work, and in other settings were examined separately. The odds ratios were highest for exposure in other settings, but they were based on a small number of positive responses. There was no consistent pattern by histologic type. Squamous cell carcinoma showed the strongest relationship with involuntary smoking, based on the husbands' smoking habits at home (RR 5.0, 95 percent C.I. 1.4, 20.1), but failed to show any relationship when involuntary smoking exposure was classified by hours of daily exposure.

This case-control study has the largest number of nonsmoking lung cancer cases to date and provides estimates of the misclassification of disease and of the smoking status of the subjects. Among the published studies on involuntary smoking, this is the only one involving independent verification of the diagnoses of all cases. This verification showed that 13 percent of the cases classified as lung cancer were not primary cancers of the lung. This study showed that 40 percent of the women with lung cancer who had been classified as nonsmokers (or smoking not stated) on hospital records had actually smoked, compared with 9 percent of the controls. The inclusion of lung cancer patients who had actually smoked would have substantially increased the odds ratios with involuntary smoking, because 81 percent of the potentially misclassified cases had husbands who smoked compared with 68 percent of the "true" nonsmoking patients with lung cancer. It should be noted that none of the other studies on involuntary smoking and lung cancer based classification of smoking status solely on data from medical records. The measure of involuntary smoking based on smoking habits of husbands attempted to differentiate between current total smoking habits and current smoking habits at home. The interview also included ETS exposure not only at home but at work and in other settings.

The exposure information presented in this study is potentially limited by its extensive reliance on surrogate interviews. Owing to the need to assemble sufficient nonsmoking cases, diagnoses as early as 1971 were included, so proxies were interviewed for a high percentage of the deceased cases. Among the cases, 12 percent of the interviews were conducted with the subject, 25 percent with the husband, 36 percent with offspring, and 27 percent with an informant who had known the subject for at least 25 years. The corresponding distribution of informants in the control series was not presented. Although the ORs did not vary consistently by respondent group, the OR for smoke exposure based on the husbands' smoking tended to be lower when husbands were the respondents. Presumably, the husbands reported their own smoking habits, and it cannot be determined whether bias resulted. The information provided by surrogates may be particularly inaccurate for exposures outside the home. Systematic bias between personal and surrogate interviews and systematic bias by informant status must also be considered. Given that the topic of involuntary smoking is potentially sensitive for the family of a lung cancer patient, it is possible that some surrogates may not have provided accurate histories, particularly with regard to their own smoking habits. Surrogate respondents for cases might have been more likely to underreport exposure than those for controls; such differential reporting would have led to an underestimation of the true effect. The multiple regression analysis performed in this study did take

respondent status into consideration, and it was determined that this factor could not account for the relationship with husband's smoking status (Garfinkel et al. 1985). It is not clear if the colorectal cancer controls were diagnosed in the same years as the lung cancer cases. Because the response patterns of relatives who are interviewed after the recent death of a subject may differ from responses obtained long after the subject has died, another source of bias may have been introduced.

A United Kingdom Study

In an ongoing hospital-based case-control study of lung cancer, chronic bronchitis, ischemic heart disease, and stroke, Lee and colleagues (1986) examined the role of involuntary smoking in a group of inpatients interviewed after 1979, when, to cover involuntary smoking, the questionnaire was extended to married patients. An attempt was also made to interview the spouses of the married nonsmoking lung cancer patients and the spouses of the comparison group.

The interview on involuntary smoking administered to hospital inpatients included questions on the smoking habits of their first spouse and on ETS exposure at home, at work, during travel, and during leisure, based on a subjective four-point scale. Spouses of nonsmokers were asked about their own smoking habits at the time of interview, during the year of admission of the subject, and during the course of their marriage.

A total of 56 lung cancer cases among married lifelong nonsmokers was identified; 2 controls were selected for each case and individually matched on nonsmoking status, sex, marital status, age, and hospital. Among the 56 cases and 112 controls, information on spouses' smoking habits was available for 29 (52 percent) cases and 59 (56 percent) controls from an interview conducted while the patient was still in the hospital. Interviews with spouses were obtained for 34 (61 percent) of the cases and 80 (71 percent) of the controls. Using both of these sources of information, the smoking habits of spouses were available for 47 (84 percent) of the cases and 96 (86 percent) of the controls. Nine risk estimates were presented for spouses' smoking, for each of the three sources of information (subject, spouse, and both), for men and women separately and for both sexes combined. The researchers concluded that spousal smoking was not associated with lung cancer, because risks were not consistently elevated. When their spouses reported about their own smoking, a RR of 1.60 (95 percent C.I. 0.44, 5.78) was found for lung cancer in the women. In contrast, a RR of 0.75 (95 percent C.I. 0.24, 2.40) was found when the female subjects reported about the smoking habits of their spouses. On the other hand, a RR of 1.01 (95 percent C.I. 0.23, 4.41) was found for male lung cancer patients when

their spouses reported about their own smoking, whereas the risk was 1.53 (95 percent C.I. 0.37, 6.34) when the male patients evaluated their spouses' smoking habits. As might be expected, the combined risk in relation to spouses' smoking for both sexes and both sources of information was near unity, at 1.11 (95 percent C.I. 0.59, 2.39). Using a second group of controls, presumably all of the nonsmokers who had responded to the hospital inpatient interview on involuntary smoking, the researchers reported no significant case and control differences in exposure to ETS at home, at work, during travel or leisure, from spouses, or for all sources combined.

This study has several limitations that must be considered in interpreting its results. Although the study attempted to verify involuntary smoking from spouses by using two sources of information, dual reports were obtained for only 16 (29 percent) of the cases and 43 (38 percent) of the controls. The questions on involuntary smoking included exposure from other sources, but they were based on a subjective scale, and different groups of controls were used for the analyses. Information was not presented on the accuracy of the diagnosis of lung cancer or on the histological types included in the study. Moreover, the investigators did not verify the smoking status of the subjects during the interviews with spouses.

The study's inconsistent findings by source of information and by sex may reflect the absence of an association between involuntary smoking and lung cancer in this population, or may reflect methodological problems in the design or conduct of the study. The main study was not originally designed to investigate the effects of involuntary smoking. However, because of interest in this issue, the investigators decided to "increase the number of interviews of married lung cancer cases and controls." The representativeness of the cases and the controls cannot be determined because there may have been differential selection factors in enrolling nonsmoking lung cancer cases and controls into the study; thus, selection bias cannot be ruled out. The method for selecting the 112 nonsmoking controls was not adequately described in the report; it is not clear whether they were selected from the pool of all controls for lung cancer or from the pool of controls for the four diseases under study. There is also an apparent discrepancy in the number of nonsmoking cases cited in the text and presented in the results. The report cited 44 never smokers among a total of 792 lung cancer patients who completed the involuntary smoking questionnaires when they were in the hospital. However, the analysis for an involuntary smoking effect based on interviews with subjects in the hospital showed only 29 lung cancer patients. This discrepancy was not explained.

The risks in relation to smoking by spouses varied with the source of information. The risk estimates tended to be higher when the respondents were men, either reporting about their own smoking

habits or the smoking habits of their spouses. This pattern could result if the male respondents overestimated exposure to environmental tobacco smoke or if the female respondents underestimated exposure. An analysis of the patients (16 cases and 43 controls) for whom data were provided by the spouses and by the subjects themselves showed a 97 percent concordance for spouses' smoking during the year of the interview and 85 percent concordance for spouses' smoking some time during the marriage. Lack of specificity in the question asked regarding spouses' smoking any time during the marriage may partly explain the discrepancy in response. To the extent that there is no consistent pattern in the direction of this discrepancy, it can be assumed that a spouse was a smoker sometime during the marriage if either respondent answered positively. On the basis of this assumption, RRs of 1.47 (spouses of 4 of 7 cases and 7 of 18 male controls smoked) and 1.39 (spouses of 8 of 9 female cases and 16 of 25 female controls) were found for the men and the women, respectively, in relation to their spouses' smoking. The risk estimates were not statistically significant, but the number of subjects was small.

The Japanese Case-Control Study

The study by Akiba and colleagues (1986) included 428 (264 men, 164 women) incident primary lung cancer cases diagnosed between 1971 and 1980 in a cohort of 110,000 Hiroshima and Nagasaki atomic bomb survivors. Controls were selected among cohort members who did not have cancer. For deceased cases, corresponding controls were selected from among cohort members who died of causes other than cancer or chronic respiratory disease. The controls were individually matched to cases on a number of factors, including age, sex, birth year (±2 years), city of residence, and vital status; a variable number of controls was interviewed, depending on the place of residence. Of the lung cancers, 29 percent were pathologically confirmed, 43 percent were radiologically or clinically diagnosed, and the remainder were found at autopsy.

Subjects or their next of kin were interviewed regarding the subjects' personal smoking, smoking habits of current spouses and parents, and occupation. Less than 10 percent of the interviews with the men and about 20 percent of the interviews with the women were conducted with the subjects themselves. The distributions of the next of kin interviewed were similar for the cases and the controls.

Among the cases, 103 (19 men, 84 women) had never smoked, compared with 380 controls (110 men, 270 women). An elevated lung cancer risk associated with smoking habits of spouses was observed for men and women. An OR of 1.8 (95 percent C.I. 0.5, 5.6) was found for nonsmoking men married to wives who smoked and an OR of 1.5

(95 percent C.I. 1.0, 2.5) for nonsmoking women married to husbands who smoked. Lung cancer risk increased with the amount smoked per day by the husband, with an OR of 2.1 for women whose husbands smoked 30 or more cigarettes per day. The OR was higher (1.8) among women who had been exposed within the past 10 years compared with those who had been exposed before that time (OR 1.3). However, an increasing duration of exposure to husbands' smoking was not associated with a monotonic trend of increasing risk. The relation between lung cancer and husbands' smoking was observed regardless of the occupation of wives (housewife, white-collar, blue-collar), but the highest odds ratio was for women who worked in blue-collar jobs and whose husbands were heavy smokers (OR 3.2).

Despite a high proportion of proxy interviews, the distribution of informant type was comparable for cases and controls; this comparability minimizes the possibility of recall bias. The high concordance between the subjects' reported smoking status in a previous survey and the information from the next of kin is reassuring. Although a high proportion of cases had no histological confirmation, an increased risk was observed regardless of the method of diagnosis. This study also provided an opportunity to test for potential confounding factors, including radiation exposure and occupation, but none were identified.

The Swedish Study

The study by Pershagen and associates (in press) included 67 incidents of primary lung cancer cases from a cohort of 27,409 nonsmoking Swedish women who were participants in a national census survey or in a twin registry. Two controls were selected from each source and were matched to cases on year of birth, and on vital status if they were selected from the twin registry.

Subjects or their next of kin (excluding husbands) were mailed a questionnaire that assessed their exposure to tobacco smoke from parents and the husband with whom the subject had lived the longest time. Information on residential and occupational history was also obtained.

Elevated lung cancer risk associated with the smoking habits of spouses was observed. For all lung cancers, ORs of 1.0, 1.0, and 3.2 were observed for women who had no, low ($\leq$ 15 cigarettes/day or $<$ 1 pack of pipe tobacco/week or $<$ 30 years of marriage), and high exposure to their husbands' smoking, respectively. The increased risk was found primarily for squamous and small cell carcinomas (OR 3.3); consistent effects could not be detected for other histologic types. On the basis of the approximately 75 percent of respondents who provided information on parental smoking, there was no effect

of parental smoking on risk for all lung cancers, after controlling for the husbands' smoking.

The study is similar in design to the Japanese case-control study (Akiba et al. 1986), except that the Swedish investigators obtained histologic confirmation for all of the cases under study. Moreover, this study excluded husbands as informants, so a potential bias associated with husbands' reporting their own smoking habits could be eliminated. The investigators contended that the finding of an association only for squamous cell and small cell carcinomas argues against a spurious finding because it is unlikely that the next-of-kin informers would have been aware of the histologic types diagnosed in the cases.

The German Study

The last in this description of studies to date based on the case-control design is a German study (Knoth et al. 1983), interpreted by the investigators as showing a role for involuntary smoking in the etiology of lung cancer. Of 39 nonsmoking women with lung cancer, 24 (62 percent) had lived with smokers. Although a comparison group was not interviewed, the investigators surmised that this frequency of smokers in the household was about three times higher than expected from census-based smoking statistics for men in the age group 50 to 69. The limitations of this study are evident; the researchers assumed that smoking prevalences for men were indicative of smoking prevalences for members of the cases' households and a specific control series was not enrolled.

Other Sources of Tobacco Smoke Exposure

Parental Smoking

Recently evaluated as a risk factor for lung cancer, parental smoking is of interest because of the large number of exposed children, the age at which it begins, and its duration. Results of this association are variable, demonstrating no association, association with just mothers' smoking, or association with both mothers' and fathers' smoking. Correa and colleagues (1983) reported an association between lung cancer risk and the mothers' smoking in the men, which persisted after adjusting for personal smoking habits (OR 1.5, $p<0.01$). This association was not observed in the women, and increased risk was not related to fathers' smoking in either the men or the women. A positive association between the mother's smoking and lung cancer risk was reported in a study of female lung cancer, but the result was not statistically significant after adjusting for personal smoking habits (OR 1.7, 95 percent C.I. 0.8, 3.5) (Wu et al. 1985). Another study suggested that the father's smoking (OR 2.5) and the mother's smoking (OR 1.8) were each related to increased

lung cancer risk after adjusting for age and individual smoking habits (Sandler, Wilcox, Everson 1985b). These results were based on small numbers, however, particularly for the mother's smoking (in 2 of 15 cases, the mother smoked). Significant associations with maternal or paternal smoking were not found in two other studies (Akiba et al. 1986; Pershagen et al. in press); however, information was lacking for about one-third of the subjects. Since smoking habits of children are highly correlated with smoking habits of parents, it is difficult, even after adjusting for personal smoking habits, to be certain that an independent effect of parental smoking has been observed.

None of the studies with data on parental smoking had sufficient numbers to examine the effects of parental smoking on nonsmokers. In Louisiana, one nonsmoking case had a mother who smoked (Correa et al. 1983). In Hong Kong, 6 percent (5/88) of the nonsmoking cases reported that their parents smoked compared with 2 percent (3/137) of the nonsmoking controls (Koo et al. 1984). In Los Angeles, the frequencies of smoking by mothers and fathers were lower for nonsmoking cases (4 percent mothers, 28 percent fathers) than for nonsmoking controls (11 percent mothers, 35 percent fathers) (Wu et al. 1985). Exposure to tobacco products during childhood was not significantly different between cases and controls (OR 0.91, 95 percent C.I. 0.74, 1.12) in another study (Garfinkel et al. 1985).

It is difficult to obtain accurate information regarding remote childhood events, so data on parental smoking tend to be crude or unavailable. Information on maternal smoking during pregnancy would not be available unless the parents could be interviewed. Because lung cancer occurs most often among older persons, an interview with a parent will generally be impossible. Moreover, information on parental smoking will most likely be unavailable or meaningless if surrogate interviews are conducted.

Coworker's Smoking

The workplace, an important source of tobacco smoke exposure, was not considered in the early studies on involuntary smoking. Later case-control studies provided some information on tobacco exposure at work, but the data were limited and inconclusive. Kabat and Wynder (1984) reported a statistically significant positive association between tobacco smoke exposure at work for men but not for women. In comparison with controls, patients with cancer in Hong Kong reported more hours and years of exposure at the workplace, but only two cases and four controls had exposure to tobacco smoke at work (Koo et al. 1984). Data in the Los Angeles study suggested that the workplace may be an important source of exposure to tobacco smoke. A small increased risk was observed for

any exposure at work, and an index combining exposure from coworkers and spouse or spouses indicated a trend of increasing risk with increasing exposure (Wu et al. 1985). Garfinkel and colleagues (1985) found no differences between cases and controls in their exposure to tobacco smoke at work during either the 5 years or the 25 years before diagnosis, and a similar lack of an association was also reported by Lee and colleagues (1986).

Dose-Response Relationship

An important factor in the appraisal of the relationship between involuntary smoking and lung cancer is the assessment of dose-response relationships. However, this analysis hinges on the definition of exposure. Data on active smoking and lung cancer suggest that exposure measures considering amount, duration, and recency of exposure should be employed in examining dose-response relationships in active smokers (Doll and Peto 1978; Pathak et al. 1986). Misclassification of exposure to ETS may be expected when exposure categorization is based on the amount or the duration of smoking by the current spouse or cohabitant, as current exposure from one source may not adequately measure past exposure or cumulative exposure. Moreover, these exposure variables may not be indicative of the exposure dose to the respiratory tract because dose determinants such as ventilation rates, breathing pattern, and deposition factors are unaccounted for.

Research is now being directed toward the integration of information from questionnaire responses, biochemical studies, and environmental sampling to determine the most accurate measures of exposure to the respiratory tract. However, exposure assessments for epidemiological studies of lung cancer and involuntary smoking will remain limited by the inaccurate recall of exposures that occurred as much as 40 to 50 years earlier. Nevertheless, research on exposure should resolve several points of uncertainty. The comparability between exposure dose measured by amount smoked and by hours or years of smoking should be assessed. The relative importance of sources of ETS should also be clarified, so there will be some agreement on whether cumulative dose should differentiate between sources of exposure.

In the absence of data showing a particular exposure measure to be optimal, an index of involuntary smoking based on the amount smoked by spouses shows the most consistent dose-response relationship with lung cancer risk (Hirayama 1981a; Trichopoulos et al. 1981; Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986). Other indices of involuntary smoking exposure have not been as well studied and have not shown a consistent dose-response relationship with lung cancer risk. These exposure variables included total years of exposure to spouses' smoking, average daily hours of exposure

from all sources, and cumulative lifetime hours and years of exposure.

Among the studies that have found a dose-response relationship with amount smoked by a spouse, three have also examined the relationship by duration of spouse's smoking (Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986), but only one study showed similarly increased risk using a dose and duration variable (Correa et al. 1983). In the study by Garfinkel and coworkers (1985), only years of smoking by the current husband or cohabitant was asked; therefore, differences in the duration of living with current husband or cohabitant may account for the less consistent dose-response relationship. In their Japanese case-control study, Akiba and colleagues (1986) suggest that intensity (amount smoked per day and recency of exposure) may be the key index of ETS in studies of lung cancer risk.

Two studies have assessed total involuntary smoking exposure to ETS. The method used by Koo and coworkers (1984) relied on respondents to describe the exposures from each source separately, and a summary measure of exposure was derived by the investigators. The method used by Garfinkel and coworkers (1985) relied on the respondents to average their exposures from all sources for specific time periods. The method of Koo and coworkers (1984) may not have adequately considered intensity of exposure; therefore, an association may have been obscured by combining low and high intensity exposures as if they were equally important. In the study by Garfinkel and coworkers (1985), a high percentage of case interviews and, presumably, control interviews was conducted with surrogates. Although information provided by surrogates regarding demographic variables is generally valid, as are responses on cigarette smoking status (current, prior, never), more detailed information on the cigarette smoking of a deceased spouse has more limited validity (Lerchen and Samet 1986). Surrogate interviews may provide adequate information about tobacco smoke exposure at home, but may be inaccurate for describing gradients of total tobacco smoke exposure from all sources.

Expected Lung Cancer Risk

An extensive data base describes the relationship between active smoking and lung cancer (US DHEW 1979, US DHHS 1982; IARC 1986). This information has been utilized to construct mathematical models to describe the relationship of dose, duration, initiation, and cessation of active smoking for risk of lung cancer. For several reasons, comparable models have not yet been developed for involuntary smoking and lung cancer. First, research on involuntary smoking and lung cancer is recent. Second, involuntary smoking is not as readily quantified as active smoking; tobacco smoke is

ubiquitous in the environment and present in variable but generally low concentrations in comparison with MS, and inhaled dose varies with ventilation and other physiological factors (Hiller 1984; Hoegg 1972; Hoffmann et al. 1984; Schmeltz et al. 1975; Stober 1984; US DHHS 1984).

Nevertheless, theoretical models, originally developed to describe the relationship of active smoking and lung cancer, have been used to predict lung cancer risk from involuntary smoking. Using Doll and Peto's (1978) model [(0.273 x 10-12) (cigarette/day + 6)^{2} (age 22.5)$^{4.5}$] for active smoking and lung cancer, Vutuc (1984) calculated expected lung cancer risks for various exposure levels, ranging from 0.1 to 5.0 cigarettes per day. For exposure levels of 0.1, 1.0, 2.0, and 5.0 cigarettes per day, the corresponding risk estimates were 1.03, 1.38, 1.78, and 3.36, respectively. These low-dose active smoking risk estimates are comparisons of active smokers with all nonsmokers (those with high ETS exposure and those with low ETS exposure). The risk estimates in involuntary smoking studies are a comparison of nonsmokers with higher levels of involuntary smoking exposure with nonsmokers who have lower levels of involuntary smoking exposure. As a result, the numerical values of the risk estimates in active smoking studies are not directly comparable to those in the involuntary smoking studies.

The appropriateness of extrapolating from the active smoking model hinges on the actual exposure of a nonsmoker. Estimates of exposure have been derived from various sources. Experimental conditions have been used to quantify the involuntary smoker's exposure to ETS. Hugod and colleagues (1978) reported that under conditions heavily polluted with sidestream smoke (to maintain a carbon monoxide concentration of 20 ppm), the particulates of tobacco smoke inhaled by involuntary smokers was small, the equivalent of one-half to one cigarette per day. Exposures may also be estimated from biochemical measurements. Studies comparing cotinine levels in nonsmokers and smokers show cotinine levels in nonsmokers that correspond to about one-sixth to one-third of a cigarette per day (Jarvis et al. 1984; Wald et al. 1984). Higher cotinine levels in nonsmokers, comparable to about two cigarettes per day, have been reported (Matsukura et al. 1984, 1985), but the results were questioned (Adlkofer et al. 1985; Pittenger 1985) and await confirmation.

The epidemiologic evidence on the lung cancer risk associated with marriage of a nonsmoker to a smoker has been criticized as implausible on the basis of predictions from Doll and Peto's model (Lee 1982a,b; Vutuc 1984). It has been argued that relative risks of 2 or 3 from involuntary smoking correspond to active smoking of two to five cigarettes per day and that this equivalent level of active smoking is too large to be realistic. This argument fails to consider

the difference in the comparison groups used to generate the risk estimates in studies of active smoking and involuntary smoking. The risk estimates for studies of active smoking use as a comparison group all nonsmokers, which includes those with and without high levels of exposure to ETS. Studies of involuntary smoking use risk estimates that are derived by comparing nonsmokers with higher levels of exposure to ETS with nonsmokers with lower levels of exposure to ETS. Because the risk estimates in active and involuntary smoking studies use different comparison groups, the numerical values are not directly comparable.

In order to make them comparable, the risk estimates in involuntary smoking and active smoking studies would have to be calculated using the same reference group. If the reference population used is all nonsmokers, then the risk estimates for nonsmokers married to nonsmokers are reduced to below 1 (i.e., their lung cancer risk would be lower than the risk for all nonsmokers as a group). The risk estimates for nonsmokers married to smokers would be above 1 (i.e., would be greater than the risk for all nonsmokers as a group), but the numerical value of the risk estimate would be reduced from the value obtained by comparison with nonexposed nonsmokers.

If the data from the Japanese cohort study (Hirayama 1981a) are recalculated to use all nonsmokers as the reference population, the risk estimate for lung cancer in nonsmoking wives of nonsmoking husbands would be 0.63 and the risk estimate for nonsmoking women married to smokers (current or former) would be 1.12. The value of 1.12 compares the risk for nonsmoking wives of smoking husbands with the risk for all nonsmokers in the studies of active smoking. This magnitude of risk is within the range of risk that would be predicted using the Doll and Peto (1978) model for calculating active smoking risk for smokers of 0.1 (risk estimate 1.03) and 1 (risk estimate 1.38) cigarette per day. The evidence for exposure to environmental tobacco smoke based on biologic markers of tobacco smoke exposure indicate that involuntary smoking exposure results in levels of biologic markers (e.g., cotinine) that are similar to levels expected in smokers of 0.1 to 1 cigarette per day. Thus, estimates derived using similar comparison groups suggest that the lung cancer mortality experience due to involuntary smoking is similar to that which would have been expected from an extension of the dose-response data for active smoking to involuntary smoking exposures.

An alternative method of estimating expected lung cancer rates has been proposed by Repace and Lowrey (1985). They compared the age-standardized lung cancer mortality rates of Seventh-Day Adventists (SDAs) who had never smoked with a demographically comparable group of nonsmoking non-SDAs and attributed the difference in lung cancer deaths solely to involuntary smoking. This

analysis was based on the following assumptions: (1) that SDAs had no exposure to passive smoking, whereas all of the non-SDAs were exposed, (2) that men and women had equal lung cancer death rates, and (3) that there were no other differences between the two groups.

Summary

Previous Reports of the Surgeon General have reviewed the data establishing active cigarette smoking as the major cause of lung cancer. The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream smoke and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer.

The quantification of the risk associated with involuntary smoking for the U.S. population is dependent on a number of factors for which only a limited amount of data are currently available. The first of these factors is the absolute magnitude of the lung cancer risk associated with involuntary smoking. As was previously described, the studies that have been performed to assess the lung cancer risk of involuntary smoking do not contain a zero-exposure group. Some exposure to tobacco smoke is essentially a universal experience; therefore, studies of involuntary smoking compare a low-exposure group with a high-exposure group. The magnitude of the risk estimate obtained is a function of the increase in risk produced by the difference in tobacco smoke exposure between the two groups examined, rather than an absolute measure of the risk of exposure in comparison with no exposure. The magnitude of the difference in tobacco smoke exposure between groups identified by spousal smoking habits may vary from study to study; this variation may partially explain the differences in risk estimates among the studies. The extrapolation of the risk estimate data to the U.S. population would therefore require a better understanding of the magnitude of the exposure to environmental tobacco smoke that occurs in the populations examined in the studies of involuntary smoking and lung cancer. Of particular interest is the magnitude of the difference in exposure between the high-exposure group and the low-exposure group.

A second set of data that would be needed to estimate the risk for the U.S. population is the dose and distribution of exposure to ETS in the population. The studies that have been performed have attempted to identify groups with different exposures, but little is known about the magnitude of the exposures that occur in different segments of the U.S. population or about the variability of exposure with time of day or season of the year. The changing norms about

smoking in public and the changing prevalence of active smoking during this century suggest that ETS exposure may have varied substantially over this century. A better understanding of the exposures that are actually occurring in the United States, and of past exposures, would be needed to accurately assess the risk for the U.S. population.

The epidemiological evidence that involuntary smoking can significantly increase the risk of lung cancer in nonsmokers is compelling when considered as an examination of low-dose exposure to a known carcinogen (i.e., tobacco smoke). Eleven of the thirteen epidemiological studies to date show a modest (10 to 300 percent) elevation of the risk of lung cancer among nonsmokers exposed to involuntary smoking; in six studies positive associations were statistically significant. The studies showing no or nonsignificantly positive findings were generally the weakest in terms of sample size (Gillis et al. 1984; Chan and Fung 1982; Koo et al. 1984; Kabat and Wynder 1984; Wu et al. 1985; Lee et al. 1986), study design (Kabat and Wynder 1984; Lee et al. 1986), or quality of data (Chan and Fung 1982).

In Table 10 are shown the sources and types of bias, and in Table 11, the statistical power, of the various case-control studies (Schlesselman 1982). On the basis of the observed relative risks reported in the studies, the respective exposure fraction in the control populations, and an a=0.05 for a two-sided significance test, only the studies by Trichopoulos and colleagues (1983) and Correa and colleagues (1983) have a probability of above 80 percent of finding a statistically significant result, whereas the majority of the case-control studies show a study power of about 0.10 to 0.20. The power of the study, as expected, improves when a one-sided significance test is considered. Among the studies in which information on involuntary smoking was available to conduct a trend test for dose, the power for detecting the observed trend was above 50 percent for five of the studies. However, the power for a two-sided test and a one-sided test, based on observed relative risk, and the power for a one-sided trend test, based on observed results, are difficult to interpret because the power is a function both of design aspects (sample size, case-control ratio, exposure prevalence) and of the observed relative risk. To focus on comparisons of the design differences between studies, the power estimates for a fixed relative risk of 2 show that five of the studies would have a power of 0.75 or greater to detect a statistically significant result. Thus, it is not surprising that some studies failed to achieve statistical significance, but the lack of statistical significance in all studies should not invalidate the positive significant associations for involuntary smoking that have been observed.

TABLE 10.—Sources and types of bias in case–control studies

Study	Author's conclusion	Misclassification of lung cancer	Misclassification of passive smoke exposure	Interviewer bias	Respondent bias
Trichopoulos et al. (1983)	Positive	+ (↓)	+ (↓)	+ (↑)	—
Correa et al. (1983)	Positive	—	+ (↓)	—	—
Chan and Fung (1982)	Negative	—	+ (↓ or ↑)	?	?
Koo et al. (1984)	Negative	—	+ (↓ or ↑)	?	?
Kabat and Wynder (1984)	Negative	—	+ (↓ or ↑)	?	?
Wu et al. (1985)	Weak positive		—	+ (↑)	—
Garfinkel et al. (1985)	Positive	—	+ (↓ or ↑)	—	+ (↓ or ↑)
Akiba et al. (1986)	Positive	+ (↓)	+ (↓)	?	+ (↓ or ↑)
Pershagen et al. (in press)	Positive	—	+ (↓ or ↑)	—	—

NOTE: Probability of misclassification: + = likely; — = not likely; ? = cannot be determined. Effect on observed risk: ↑ = overestimated risk as result of bias; ↓ = underestimated risk as result of bias.

Six epidemiological studies found statistically significant increased risks associated with spouse's smoking; all demonstrated a dose-response relationship, and several suggested a stronger association with squamous cell and small cell carcinoma than with other cell types. Three of these studies (Hirayama 1984a; Correa et al. 1983; Akiba et al. 1986) included nonsmoking male lung cancer patients, and the complementary findings in nonsmoking husbands married to smoking wives strengthen the evidence on involuntary smoking. The four studies with significant positive findings published since 1981 (Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986; Pershagen et al., in press) not only corroborated the findings of Hirayama (1981a) and Trichopoulos and colleagues (1981), but answered the many criticisms directed at these two studies.

TABLE 11.--Study power for case-control study based on an unmatched analysis

Study	Number of cases	Control: case ratio	Proportion of controls' spouses who smoked	Observed relative risk for ever vs. never exposed to spouses smoking	Power for two-sided test based on observed RR	Power for one-sided test based on observed RR	Power for one-sided trend teat based on observed results[1]	Power for one-sided test based on RR=2 for ever vs. never exposed
Trichopoulos et al. (1983)	77	2.92	0.52	2.11	0.79	0.87	0.88	0.88
Correa et al. (1983)	30	10.43	0.28	2.97	0.83	0.88	0.97	0.55
Chan and Fung (1982)	84	1.66	0.48	0.75	0.17	0.26	NA[2]	0.80
Koo et al. (1984)	88	1.56	0.71[3]	1.23	0.10	0.17	0.10	0.64
Kabat and Wynder[4] (1984)	36	1.03	0.54	0.85	0.05	0.10	NA[2]	0.39
Wu et al.[5] (1985)	28	1.96	0.60	1.41	0.10	0.17	0.16	0.37
Garfinkel et al. (1985)	134	3.00	0.61	1.23	0.24	0.36	0.71	0.94
Lee et al. (1986)	47	2.04	0.62	1.11	0.04	0.08	NA[2]	0.52
Akiba et al.[6] (1986)	84	2.96	0.67	1.47	0.26	0.38	0.53	0.75

TABLE 1l.--Continued

Study	Number of cases	Control: case ratio	Proportion of controls' spouses who smoked	Observed relative risk for ever vs. never exposed to spouses' smoking	Power for two-sided test based on observed RR	Power for one-sided test based on observed RR	Power for one-sided trend teat based on observed results[1]	Power for one-sided test based on RR=2 for ever vs. never exposed
Pershagen et al. (in press)	67	5.18	0.44	1.23	0.12	0.19	0.46[7]	0.83
Pooled[8]	676	2.96	0.52	1.53	0.99	1.00	NA	1.00
Pooled[9]	509	3.40	0.52	1.88	1.00	1.00	1.00	1.00

[1]Based on three levels of passive smoke exposure as defined in respective studies.
[2]Data not available for trend test.
[3]Includes spouses, cohabitants, and coworkers who smoked.
[4]Based on nonsmoking cases and controls with information on spouses' smoking.
[5]Based on cases and controls who were ever married.
[6]Based on female cases and controls with information on husbands' smoking (number of cigarettes smoked per day).
[7]Estimate based on 26 cases and 151 controls in the low exposure category, 7 cases and 12 controls in the high exposure category
[8]Based on combined results of the 10 case-control studies.
[9]Based on combined results of the seven case-control studies with data available for trend test.

The most serious criticism is the misclassification of the active smoking status of the subjects, which can produce an apparent increased risk with involuntary smoking. Moreover, it is likely to result in differential misclassification because spouses tend to have similar smoking habits (Burch 1981; Sutton 1981; Higgins et al. 1967). Speculation that the positive results reported in Japan and Greece were due to cultural bias against the admission of smoking by women in these more traditional societies may be discounted because positive significant findings have now been observed in the United States (Correa et al. 1983; Garfinkel et al. 1985) and in Sweden (Pershagen et al., in press), where no comparable social stigma exists. Moreover, in the studies by Garfinkel and coworkers (1985) and Pershagen and coworkers (in press), the personal smoking status of each subject was validated and verified at interview, usually by next of kin, who presumably would have no reason to misrepresent the true smoking status of the subject.

Misclassification of the lung as the primary site and the lack of pathological confirmation are repeated concerns, but it must be stressed that this bias would tend to dilute a true effect. Correa (1983), Garfinkel (1985), and Pershagen (in press) and their respective colleagues addressed this issue by including only pathologically confirmed lung cancers and considering histological cell type in their analyses. In the study by Garfinkel and associates (1985), after an independent pathological review was conducted, a significant association of excess risk with involuntary smoking remained. Misclassification of exposure to ETS cannot be dismissed, since an index based solely on the smoking habits of a current spouse may not be indicative of past exposure, cumulative exposure, or the relevant dose to the respiratory tract.

The magnitude of risk associated with involuntary smoking exposure is uncertain. Relative risks ranging from 2 to 3 were generally reported for the highest level of exposure based on the spouses' smoking habits, but since sample sizes in most studies are not large, the point estimates of effect are unstable, and confidence limits are broad and generally overlap from one study to another. An index of involuntary smoking based on the smoking habits of the spouse is a simplistic and convenient measure. There is no reason to believe, however, that the excess risk associated with involuntary smoking is restricted to exposure from spouses. Nonsmokers married to smokers are likely to be more tolerant of ETS exposure and to experience more exposure to environmental tobacco smoke (Wald and Ritchie 1984). Higher risk estimates for involuntary smoking have been obtained in studies restricted to squamous cell and small cell carcinomas of the lung.

Although involuntary smoking can be established as a cause of lung cancer, important questions related to this exposure require

further research. More accurate estimates for the assessment of exposure in the home, workplace, and other environments are needed. Studies of sufficiently large populations should also be performed. New data from such studies should yield more certain risk estimates and describe the magnitude of the lung cancer risk in nonsmokers.

Other Cancers

Several recent studies provide data on the relationship of ETS exposure to cancer at sites other than the lung. Two published reports address the risk of other cancers in adults from exposure to tobacco smoke from spouses. Using the same Japanese cohort described previously, Hirayama (1984a) reported excess mortality for cancers of the paranasal sinus (N=28) and brain (N=34) among nonsmoking women who were married to smokers. The standardized mortality ratios (SMRs) for nasal sinus cancer were 1.00, 1.67, 2.02, and 2.55 for women whose husbands never smoked, or had smoked 10 to 14, 15 to 19, or 20 or more cigarettes per day, respectively (one-sided p for trend, 0.03). The corresponding SMRs for brain tumors were 1.00, 3.03, 6.25, and 4.32, respectively (one-sided p for trend, 0.004). The total number of deaths due to nasal cancer and brain tumors was small, and the numerators in the risk calculations were unstable, based on five nasal cancers and three brain cancers in women whose husbands were nonsmokers. In one study (Brinton et al. 1984), active tobacco smoking was associated with an increased risk of sinus cancer, particularly squamous cell tumors. Sidestream smoke has also been suggested to be of etiological importance in brain tumors in children (Preston-Martin et al. 1982).

In a case-control study of adult cancers in relation to childhood and adult exposure to involuntary smoking, Sandler and coworkers (1985a, 1986) reported an overall cancer risk of 1.6 (95 percent C.I. 1.2, 2.1) associated with exposure to spouses' smoking, which was more marked in nonsmokers than smokers. Significant increases were observed for cancer of the breast (OR 1.8), cervix (OR 1.80, and endocrine organs (OR 3.2). This study has been criticized in its choice of controls and in the exclusion of certain cancers by the design of the study. The biological plausibility of the study's findings was also questioned because the highest risk estimates were observed for cancers that have not been consistently related to active smoking and because higher risks were observed for nonsmokers than for smokers. Failure to control for potential confounding factors and known risk factors for the individual cancer sites under study may have produced artifactual results (Friedman 1986; Mantel 1986; Burch 1986). In a subsequent analysis of the same study population, Sandler, Wilcox, and Everson (1985a,b) reported increasing cancer

risks with increasing exposure to involuntary smoking as measured by the number of smokers in the household and by the time periods of exposure. The biologic plausibility of these findings was also questioned (Burch 1985; Higgins 1985; Lee 1985).

The effect of parental smoking on the development of cancers both during childhood and in adult life is also of interest. The relationship of parental smoking to overall cancer risk in children or in adults has been assessed in three studies. A prospective survey (Neutel and Buck 1971) of about 90,000 infants in Canada and the United Kingdom followed for a maximum of 10 years found an overall cancer risk of 1.3 (95 percent C.I. 0.8, 2.2) associated with maternal smoking during pregnancy. No dose-response relationship was observed, but there were few heavy smokers (> 1 pack/day) in this study. A Swedish case-control study (Stjernfeldt et al. 1986) of all cancers found a risk of 1.4 (95 percent C.I. 1.0, 1.9) for maternal smoking during pregnancy. A dose-response relationship was demonstrated; the risk was highest in the most exposed group, those smoking 10 or more cigarettes per day (RR 1.6, $p < 0.01$). On the basis of the smoking habits of the parents of subjects up to 10 years of age, Sandler, Everson, Wilcox, and Browder (1985) reported no significant difference between all cancer cases and controls with respect to the mother's smoking (RR 1.1, 95 percent C.I. 0.7, 1.6), but the father's smoking was related to an overall increased risk (RR 1.5, 95 percent C.I. 1.1, 2.0). In these three studies, analysis by specific cancer site revealed an increased risk of leukemia associated with parental smoking.

Neutel and Buck (1971) found an almost twofold increased risk of leukemia in children of mothers who smoked during pregnancy, but the association was not statistically significant. Stjernfeldt and colleagues (1986) reported a significant positive association between maternal smoking and acute lymphoblastic leukemia. The relative risks were 1.0, 1.3, and 2.1 (p for trend, <0.01) for mothers who smoked 0, 1 to 9, and 10 or more cigarettes per day, respectively. Similar significant positive associations with maternal smoking were not observed for other cancer sites, but the risk assessments were based on a small number of cases. This study suggests that the relationship between maternal smoking and leukemia was strongest for smoking during the 5-year period before pregnancy, intermediate for smoking during pregnancy, and lowest for smoking after pregnancy. In the study by Sandler, Everson, Wilcox, and Browder (1985), the mother's smoking and the father's smoking were separately and jointly associated with an increased risk for leukemia and lymphoma. The relative risk was 1.7 when one parent smoked and 4.6 when both parents smoked (p for trend, <0.001). The increased risk with parental smoking was observed regardless of the personal smoking status of the subject. No other cancer site was associated

with the mother's smoking, although the father's smoking was associated with increased risks for other cancer sites, including the brain and the cervix. Two studies of leukemia in children found no relationship with parental smoking (Manning and Carroll 1957; Van Steensel-Moll et al. 1985). In the study by Manning and Carroll (1957), the mothers' general smoking habits were assessed, whereas Van Steensel-Moll and colleagues (1985) obtained information on the smoking habits of both parents in the year before the pregnancy. Stewart and colleagues (1958) reported a statistically significant risk of 1.1 ($p=0.04$) for leukemia in association with the mothers' smoking, but cautioned that the smoking information on the mothers pertained to their habits at the time of interview, which took place after the deaths of the patients and may have been affected by bereavement.

The effect of parental smoking habits has been examined in epidemiological studies of brain tumors, rhabdomyosarcoma, and testicular cancer in children. Gold and colleagues (1979) reported an association between maternal smoking prior to and during pregnancy and brain tumors in children. A relative risk of 5.0 ($p=0.22$) was found, but the result was based on a small number of patients and was not statistically significant. No relationship between maternal smoking during pregnancy (RR 1.1, one-sided $p=0.42$) and brain tumors in children was found in another study (Preston-Martin et al. 1982), but a significantly increased risk (RR 1.5, one-sided $p=0.03$) associated with mothers living with a smoker (usually the child's father) during pregnancy was observed. A significantly increased risk with the father's smoking, but not the mother's smoking was also reported in a study of rhabdomyosarcoma (Grufferman et al. 1982). The father's smoking conferred a significant increase in risk (RR 3.9, 95 percent C.I. 1.3, 9.6), but the mother's smoking during and after the pregnancy was not significantly different between cases and controls (RR 0.8, 95 percent C.I. 0.3, 2.0). A history of maternal smoking during pregnancy did not differ for testicular cancer cases and controls (RR 1.0, $p=0.57$) in one study (Henderson et al. 1979).

There are at present insufficient data to adequately evaluate the role of involuntary smoking in adult cancers other than primary carcinoma of the lung. In addition, active smokers necessarily receive greater exposure to ETS than nonsmokers. Thus, effects would not be anticipated in involuntary smokers that do not occur in active smokers (IARC 1986), and the biological plausibility of associations between ETS exposure and cancer of sites not associated with active smoking must be questioned. The findings of Hirayama (1984a) and Sandler, Everson, and Wilcox (1985) need confirmation in studies that take into account the potential confounding factors and the known risk factors for these individual sites. The evidence

for parental smoking and childhood cancer is also not clear, and evaluation of this association is made difficult by the various definitions of exposure that have been used, including maternal and paternal smoking before, during, and after the pregnancy. Mothers and fathers who smoke during a pregnancy generally smoked before the conception and continue to smoke after the pregnancy. Thus, an effect of involuntary smoking after birth cannot readily be distinguished from genetic or transplacentally mediated effects.

Cardiovascular Diseases

A causal association between active cigarette smoking and cardiovascular disease is well established (US DHHS 1983). The relationship between cardiovascular disease and involuntary smoking has been examined in one case-control study and three prospective studies. In the case-control study by Lee and colleagues (1986), described previously, ischemic heart disease cases and controls did not show a statistically significant difference in their exposure to involuntary smoking, based on the smoking habits of spouses or on an index accounting for exposure at home, at work, and during travel and leisure. In the Japanese cohort study, Hirayama (1984b, 1985) reported an elevated risk for ischemic heart disease (N=494) in nonsmoking women married to smokers. The standardized mortality ratios when the husbands were nonsmokers, ex-smokers or smokers of 19 or more cigarettes per day, and smokers of 20 or more cigarettes per day were 1.0, 1.10, and 1.31, respectively (one-sided p for trend, 0.019).

In the Scottish followup study (Gillis et al. 1984), nonsmokers not exposed to tobacco smoke were compared with nonsmokers exposed to tobacco smoke with respect to the prevalence of cardiovascular symptoms at entry and mortality due to coronary heart disease. There was no consistent pattern of differences in coronary heart disease or symptoms between nonsmoking men exposed to tobacco smoke and their nonexposed counterparts. Nonsmoking women exposed to tobacco smoke exhibited a higher prevalence of angina and major ECG abnormality at entry, and also a higher mortality rate for all coronary diseases. However, rates of myocardial infarction mortality were higher for exposed nonsmoking men and women compared with the nonexposed nonsmokers. The rates were 31 and 4 per 10,000, respectively, for the nonexposed nonsmoking men and women, and 45 and 12 per 10,000, respectively, for the exposed nonsmoking men and women. None of the differences were tested for statistical significance.

In the Japanese and the Scottish studies, other known risk factors for cardiovascular diseases, i.e., systolic blood pressure, plasma cholesterol, were not accounted for in the analysis.

In a study of heart disease, Garland and coworkers (1985) enrolled 82 percent of adults aged 50 to 79 between 1972 and 1974 in a predominantly white, upper-middle-class community in San Diego, California. Blood pressure and plasma cholesterol were measured at entry, and all participants responded to a standard interview that asked about smoking habits, history of heart disease, and other health-related variables. Excluding women who had a previous history of heart disease or stroke or who had ever smoked, 695 currently married nonsmoking women were classified by their husbands' self-reported smoking status at enrollment. After 10 years of followup, there were 19 deaths due to ischemic heart disease; the age-standardized mortality rates for nonsmoking wives whose husbands were nonsmokers, ex-smokers, and current smokers were 1.2, 3.6, and 2.7, respectively (one-sided p for trend, $\leq$ 0.10). After adjustment for age, systolic blood pressure, total plasma cholesterol, obesity index, and years of marriage, the relative risk for death due to ischemic heart disease for women married to current or former smokers at entry compared with women married to never smokers was 2.7 (one-sided $p \leq 0.10$).

The study's findings are not convincing from the point of view of sample stability. The total number of deaths due to ischemic heart disease was small, and the denominator in the relative risk calculation is unstable, based on the deaths of two women whose husbands had never smoked. Moreover, it is well established that the risk of coronary heart disease is substantially lower among those who have stopped smoking (US DHHS 1983), although the amount of time required for this change after cessation of smoking is not clear (Kannel 1981). In this study, 15 of 19 deaths occurred in nonsmoking women married to husbands who had stopped smoking at entry, and the age-standardized rate for ischemic heart disease was highest in this group. The high proportion of deaths in nonsmoking women married to men who became ex-smokers implies that the excess resulted from a sustained effect of involuntary smoking. More detailed characterizations of exposure to ETS and specific types of cardiovascular disease associated with this exposure are needed before an effect of involuntary smoking on the etiology of cardiovascular disease can be established.

One study (Aronow 1978a,b) suggested that involuntary smoking aggravates angina pectoris. This study was criticized because the end point, angina, was based on subjective evaluation, and because other factors such as stress were not controlled for (Coodley 1978; Robinson 1978; Waite 1978; Wakehan 1978). More important, the validity of Aronow's work has been questioned (Budiansky 1983).

Conclusions

1. Involuntary smoking can cause lung cancer in nonsmokers.
2. Although a substantial number of the lung cancers that occur in nonsmokers can be attributed to involuntary smoking, more data on the dose and distribution of ETS exposure in the population are needed in order to accurately estimate the magnitude of risk in the U.S. population.
3. The children of parents who smoke have an increased frequency of hospitalization for bronchitis and pneumonia during the first year of life when compared with the children of nonsmokers.
4. The children of parents who smoke have an increased frequency of a variety of acute respiratory illnesses and infections, including chest illnesses before 2 years of age and physician-diagnosed bronchitis, tracheitis, and laryngitis, when compared with the children of nonsmokers.
5. Chronic cough and phlegm are more frequent in children whose parents smoke compared with children of nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study.
6. The children of parents who smoke have small differences in tests of pulmonary function when compared with the children of nonsmokers. Although this decrement is insufficient to cause symptoms, the possibility that it may increase susceptibility to chronic obstructive pulmonary disease with exposure to other agents in adult life, e.g., active smoking or occupational exposures, needs investigation.
7. Healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone.
8. A number of studies report that chronic middle ear effusions are more common in young children whose parents smoke than in children of nonsmoking parents.
9. Validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments.
10. The associations between cancers, other than cancer of the lung, and involuntary smoking require further investigation before a determination can be made about the relationship of involuntary smoking to these cancers.
11. Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to

determine whether involuntary smoking increases the risk of cardiovascular disease.

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