Pediatricians have considered tobacco smoke exposure in the troubled allergic child an identifiable problem to be faced. McGovern and coworkers (*70*) emphasized that allergic disease represents a major school health problem because children with hay fever, allergic rhinitis, and asthma account for about one-third of all chronic conditions reported under age 17. A survey is cited in which it was noted that asthma accounted for 11.4 percent of all chronic conditions in children and for 22.9 percent of days lost from school (*8*). These clinical investigators have, therefore, emphasized the need and value of removing the allergic child from all environmental sources of tobacco smoke exposure as a valid preventive measure.

Since the chances for progression of disease are more likely to occur in the face of continued and uncontrolled presence of causative factors, the potential for chronicity among adults is evident. The magnitude of the problem can be appreciated by noting the large population surveys in the United States which estimate that as many as 15 to 17 percent of the population suffers from asthma or hay fever (*97*). Thus, to whatever extent tobacco and/or tobacco smoke play a causal or contributory role in allergy, if they are ultimately shown to be allergens, it would be important for allergic patients of all age groups to take appropriate precautions to avoid exposure.

Effects of Cigarette Smoking on the Immune System

That cigarette smoking can affect the immune system has been well documented in both animals and humans. For purposes of discussion, these alterations in immune function can be classified as local and systemic. The local host defense system is comprised of the mucociliary mechanisms and functionally specialized cells, such as the macrophages and lymphocytes. Systemic defense mechanisms divide conveniently along the lines of cellular and humoral immunity.

Microscopic examinations of the respiratory tract mucosa demonstrate that chronic smoking leads to denuding of the ciliated epithelium, an increased number of goblet cells, and squamous metaplasia (*89*). On the other hand, studies attempting to quantify toxicity of cigarette smoke to cilia have been difficult to evaluate because of variation of mucus transport rates both among and within species studied, differences in techniques used to measure ciliary activity, and variations in methods and periods of exposure employed.

Studies on the short-term effects of smoke on ciliary function *in vitro* and *in vivo* generally show decreased function. Ciliostasis has been produced by *in vitro* exposure of the epithelium of the human respiratory tract to smoke residue passed through an aqueous medium (*7*) and, along with decreased rates of mucus transport, has also been observed in many animal models (*1, 26, 50, 55*). However, the effects of short-term smoking on mucociliary function in man have been

contradictory. In studies by Yeates, et al. (*128*) which measured mucociliary tracheal transport rates, some smokers showed slower bronchial clearance rates, while others showed little or no change over nonsmokers. Camner and coworkers (*17*), on the other hand, found mucociliary transport to be significantly increased during periods of intensive smoking (to the point of discomfort) compared to nonsmoking periods.

Studies of long-term exposure have also been undertaken and, again, both animal and human studies are contradictory. Two studies were carried out in dogs exposed to forced smoke inhalation. One showed no change in tracheobronchial clearance (*6*) while the second, by different methodology, showed that tracheal mucus velocity was 30 percent of that found in controls (*118*).

In a study of 10 pairs of identical twins, discordant with regard to smoking (*16*), five of the smoking twins had decreased clearance rates while the other five demonstrated no differences over controls. Similarly, Albert, et al. (*2*) found bronchial clearance impaired in 8 out of 14 cigarette smokers tested. Lourenco and coworkers (*65*) found delayed clearance of particles, particularly in the central airways, at 1 hour after inhalation in nine smokers when compared to controls. On the other hand, Pavia, et al. (*82*) found no decrease in the efficiency of removal of particulate matter in the lungs of smokers compared to nonsmokers. However, the evidence indicates an adverse effect of long-term smoking on the mucociliary transport mechanisms and mucus composition (*58*).

It is necessary to understand the functions of alveolar macrophages and lung phagocytic cells as well as the population of immunocompetent lymphocytes in pulmonary tissue in order to appreciate how these elements and their modification can affect the processing of tobacco antigen and the resultant production of antibody and cell-mediated immunity. Since hypersensitivity phenomena are products of the immune system, these cellular elements can serve as determinants of allergic inflammation as well as of immunity.

Alveolar macrophages are important to lung function because of their role as phagocytes, engulfing and digesting particulate matter in the lung. Also, these cells process antigens and interact with lymphocytes in immune and allergic processes.

Many studies have examined the effect of smoking on macrophage function and metabolism. Even though most of these are *in vitro* studies, comparison is difficult because of differences inherent in the human and animal models used. In addition, in some cases, human subjects or animals were exposed to the smoke before the cells were harvested, while in others, cells were exposed directly to the smoke. Other variables included serious differences in amounts and lengths of exposures, filtration of smoke, and different methods of harvesting

cells. Nevertheless, it is clear from these studies that profound alterations in macrophages result from smoke exposure.

One consistent finding concerning the effect of smoking on macrophages is that the total number is increased in smokers. Keast and Holt (*57*) used a special apparatus simulating human smoking in exposed mice. They found initial and sustained elevations in macrophage populations. Other workers (*56*) also found increased macrophage numbers after only 2 weeks of cigarette smoking in humans. Studies by Pratt, et al. (*88*) and Harris, et al. (*44*) showed that smokers had strikingly increased numbers of macrophages when compared to nonsmokers and, furthermore, that macrophages accounted for 90 to 95 percent of lavaged lung cells found in smokers. The authors (*44*) speculate that increased alveolar macrophages in smokers might play an important role in pulmonary defense against toxic components of cigarette smoke. Also important is the possibility that macrophage accumulations could contribute to the pathogenesis of chronic pulmonary disease by the release of lysosmal enzyme content.

Changes in ultrastructure of macrophages have also been reported in smokers. Pratt and associates (*88*) observed that macrophages obtained in lung fluids of smokers were filled with cytoplasmic inclusions, and Martin (*67*) identified multinucleated giant cells in some smokers but none in nonsmokers. Martin (*67*) also noted that crystalloid refractile cytoplasmic inclusions were more common among the smokers. Harris, et al. (*44*) found the most salient feature of the macrophages from smokers to be larger and more numerous lysosomal bodies.

The study by Holt and Keast (*47*) demonstrated that the immediate toxic effects of tobacco smoke *in vitro* were greater in macrophages than fibroblasts, with surviving macrophages showing an increase in measured protein synthesis. Keast and Holt (*57*) also found that the macrophages from mice exposed to smoke for many weeks were no longer as susceptible to the untoward effects of smoke and had apparently adapted to the toxic conditions in a fashion similar to that seen in the tissue culture experiments.

Enzyme systems have also been shown to be affected by smoking. Martin (*67*) demonstrated that increased macrophage acid hydrolase directly correlated with daily cigarette consumption. Meyer, et al. (*72*) examined the effect of various concentrations of nicotine on the ATPase activity of sheep pulmonary alveolar macrophages and showed significant inhibition of this activity. Additionally, lower concentrations of this alkaloid stimulated cell respiration while higher concentrations were inhibitory. Kasemir and Kerp (*56*) recorded decreased oxygen uptake in sheep macrophages in contact with tobacco extracts. The *in vitro* studies of Harris and coworkers (*44*) on human alveolar macrophages demonstrated increased glucose utilization in smokers.

In pertinent studies, macrophage function has been measured by several methods. Green and Carolin (*34*), using an *in vitro* system to

measure phagocytosis, showed that added cigarette smoke had a depressant effect on the phagocytic activity of alveolar macrophages for *Staphylococcus albus*. The studies by Maxwell, et al. (*69*) on lung macrophages from guinea pigs exposed to tobacco prior to cell harvest showed that, although these alveolar cells phagocytosed bacteria at normal rates, their capacity for bacterial inactivation was impaired.

Laurenzi, et al. (*61*) demonstrated a 50 percent reduction in clearance of staphylococci from the lungs of smoke-exposed mice. In two human studies (*22, 44*) which measured phagocytic properties of alveolar macrophages, no significant differences were found between smokers and nonsmokers. Other studies of *in vitro* function of macrophages after *in vivo* exposure to smoke (employing rat alveolar macrophages) revealed no impairment of bactericidal inactivation of *S. albus* (*49*).

In the studies of Warr and Martin (*119, 120*), macrophages of smokers demonstrated an impaired response to an immune effector, MIF, paralleling those situations characterized by the absence of cell-mediated delayed hypersensitivity as well as acquired resistance to aggregate under *in vitro* conditions.

Though more work is needed to define the total qualitative and quantitative influences of tobacco smoking on alveolar macrophages, there is sufficient evidence in these studies to indicate measurable degrees of physiological impairment. Since interference with phagocytosis, endocytosis, and antigen processing can be anticipated as a consequence, there is the potential diminution of specific immune functions by these cells. In turn, the impairment of local immune processes as the first line of host defense exerts its toll on the dependent development of systemic immunity and influences emerging allergic inflammation.

The B and T lymphocytes are involved respectively in the humoral and cell-mediated arms of the immune system that functions both locally and systemically. It is therefore pertinent to examine the effect of smoking on these elements that provide the immunologic basis of hypersensitivity.

Of the immunoglobulins, secretory IgA is known to be predominant in bronchial mucus (*29*) (although the IgG/IgA ratio is increased in smokers (*90*)) and presumably plays a role in first-line defense against microbial invasion. Soutar's (*101*) studies on the distribution of plasma and other immunoglobulin-containing cells in the respiratory tract indicated more IgA-containing cells then those of other immunoglobulin classes. However, the only differential finding between smokers and nonsmokers was localized to the lobar bronchi of smokers where significant increases in IgA-containing cells were identified. Smoking was found to have significant suppressive action on salivary secretory IgA levels in normals, but not in patients with chronic diseases whose IgA levels were already elevated above normal (*63*). While these

studies show alterations in the expressions of local humoral immunity, the clinical significance of these changes is unknown.

Investigations have also been done to determine the effect of smoking on systemic humoral immunity. An assay which reflects antibody production is the plaque-forming cell (PFC) response. Thomas, et al. (*108*) examined PFC responses in samples of immunocompetent lung cells from mice exposed to fresh cigarette smoke and found progressive impairment of these responses over the exposure period of up to 10 months. In the studies of Holt, Keast, Nulsen, and Thomas (*76,106,108,109,110*) concerning the long-term effects of smoking on mice, PFC responses to intratracheally or intraperitoneally introduced antigens were shown to be initially enhanced and then depressed by chronic smoking (*108,109*). The direct measurement of serum hemolytic and hemagglutinating antibodies also showed depression, but the humoral response to a T cell-independent immunogen was unaffected (*109*). The secondary PFC response reflecting another aspect of humoral immunity was unaffected by smoking (*109*). PFC response depression was found to be reversible in a group when smoking was discontinued for 16 weeks (*110*). Other measurements of humoral immunity in mouse models exposed to tobacco also demonstrated impairment of the production of hemagglutinating antibodies, including those raised in response to the influenza virus (*66*), although some degree of suppression was reversible (*28*). Tar content of cigarettes may also play an important role (*46*).

Roszman, et al. (*93, 94, 95*), investigating several aspects of smoking and immunity in rabbits, found suppression of mitogen-induced blastogenesis and suppression of the immunoglobulin M and G antibody responses which correlated directly with the concentration either of nicotine or of the water-soluble fraction from cigarette smoke that was added to cultures.

Several surveys have attempted to address the issue of whether smoking influences serum immunoglobulin levels. Vos-Brat and Ruemke (*116*) found significant depression of IgG in smokers, Kosmider, et al. (*59*) also found a decreased IgG but increased IgM and IgA, while Wingerd and Sponzilli (*127*) found a decrease in the entire gamma globulin fraction. A decrease in lymphocytotoxic antibodies among smokers has also been demonstrated in pregnant women (*77*). On the other hand, no reported differences in mean concentrations of immunoglobulins were found when smokers were compared to nonsmokers by geographic location (*71*).

While these reports suggest that humoral antibody responses are influenced by cigarette smoke in a variety of ways, critical to this issue is a consideration of possible biologic impact in humans. Whether susceptibility to infection may be the end result of smoking effects on constituent elements of the immune system should be addressed. Thus, especially pertinent are the influenza vaccination studies of Waldman,

et al. (*117*), indicating that smoking more than one-half pack of cigarettes per day increased the risk of influenza-like illness, although the duration of the illness was unaltered. Finklea and associates (*32*) showed that the incidence of clinical influenza was 21 percent higher among smokers than nonsmokers. Serological data from this study suggested that smokers also had more frequent subclinical influenza. In pursuing this observation, Finklea, et al. (*31*) showed that, while serologic response to vaccination did not significantly differ between smokers and nonsmokers, the persistence of antibody titers after either natural infection or vaccination with A_2 antigens was significantly decreased among smokers. Nymand (*77*), examining histories of pregnant women, found that urinary tract infections and viral illness were observed more often in smokers than nonsmokers.

That elements indicative of immune function appear in the lung is evidenced by the identification of both T and B cells in fluid samples recovered from this site (*121*). Of interest is the finding of both an increased number of T and B cells and an increase in the T/B ratio in smokers.

Several aspects of cell-mediated immunity have been studied in animal models, including the ability of immunocompetent lymphocytes to proliferate after mitogenic stimulation by phytohemagglutin (PHA), pokeweed (PW), and Concanavalin A (Con-A). In mice, initial increases of PHA responses in blood and regional lymph node lymphocytes were found after brief exposure to cigarette smoke, but decreases were found after prolonged exposure (*107*). Another study (*18*) demonstrated inhibition of proliferation of mouse lymphocytes to both PHA and pokeweed mitogen by an aqueous fraction of tobacco. In the rabbit (*94*), both nicotine and water-soluble fractions from whole cigarette smoke diminished peripheral lymphocyte blastogenic response to lectin stimulation.

Because of variation in methodology, data from human studies are difficult to compare. While increased numbers of T cells in peripheral blood lymphocytes and enhanced PHA response were noted among younger smokers, responses of older smokers or of those with a history of heavier cigarette consumption did not differ from normals (*100*). In examining peripheral bloods, Suciu-Foca, et al. (*103*) found no differences in percent of T lymphocytes, PHA responses, or behavior in mixed lymphocyte cultures between smokers and nonsmokers. In another study (*125*), samples of blood taken from humans after smoking showed no differences in PHA responses even when physiologic levels of nicotine were added directly to the cultures. In contrast, Neher (*74*) found decreased DNA synthesis in response to PHA in the presence of nicotine. Desplaces, et al. (*27*) showed that smoke inhibited lymphocyte transformation by PHA yet stimulated lymphocytes in the absence of PHA. The clinical significance of this single aspect of T-cell function has yet to be determined.

Effects on other cellular elements of the immune system have also been described. Vos-Brat and Ruemke (*116*) and Silverman, et al. (*100*) demonstrated increased granular leukocytic levels in smokers. Others (*54,79,98,129*) have shown that smokers have hypereosinophilia. In two studies (*79,98*) the hypereosinophilia was reversible with abstinence from smoking. Similar lymphocytic and eosinophilic increases among smokers have been noted in patients' post-myocardial infarctions (*129*).

Serum abnormalities also have been described in smokers, including increased C-reactive (*45*) protein and an abnormal seroflocculant in smokers. Effects of smoking on manifestations of immune hyperresponsiveness add further evidence to the purported suppressive action of tobacco. Of interest are the reports of diminution of amyloid formation in the hamster model (*123*) and the inexplicable increase in survival of cardiac transplants in patients who resumed smoking postoperatively (*35*).

Target Organs of the Allergic Response

Despite the limitations, as previously noted, in appropriate materials and methods to define any possible effects of tobacco and smoking on allergic people, studies dealing with their roles in affecting various organs are noteworthy. A variety of clinical conditions have been ascribed to allergic manifestations to tobacco leaf or smoke, including asthma, rhinitis, hives, dermatitis, migraine headaches, cardiac and other vascular disturbances, as well as gastrointestinal disorders. The respiratory system has been the most widely studied.

Allergic rhinitis, typified by hay fever due to seasonal pollens and molds, is caused by exposure to a wide range of ubiquitous allergens. Apart from investigations of tobacco workers, there are no available studies to date to suggest that tobacco smoke or tobacco allergens are in fact a cause of allergic rhinitis in the general population. Many studies, however, have been reported showing that rhinitis patients suffer exacerbation of symptoms upon exposure to smoke. Speer (*102*) reported that 67 percent of allergic persons noted aggravation of nasal symptoms upon exposure to smoke, compared to 29 percent of nonallergic persons similiarly exposed. Broder, et al. (*11*) found that most symptoms of allergic rhinitis could be attributed to other definable allergens with smoking or smoke exposure playing only a minor role. Allergic rhinitis believed to be related specifically to hypersensitivity to tobacco leaf products was reported to occur in 14.6 percent of 355 tobacco plantation workers and 8.7 percent of 722 tobacco factory workers (*114*).

Another study (*86*) among tobacco workers demonstrated that allergic rhinitis thought to be related to tobacco leaf occurred in approximately 4 percent of cases. However, possible contamination of

tobacco by molds or other allergens or irritants was not excluded in these studies.

It is relevant to note that symptoms of nasal congestion and excess mucous gland secretion, which may mimic those of allergic rhinitis or hay fever, can be caused by the nonspecific irritant or pharmacologic effects of vapor from the constituents of tobacco smoke. Thus, although it is not known whether allergy to tobacco or tobacco smoke plays a primary etiologic role in the usual case of allergic rhinitis, tobacco smoke per se is known to aggravate this condition via an irritant effect.

It is well known (*102*) that eye irritation manifested by itching, burning, swelling, and lacrimation occurs commonly among both allergic nonsmokers and nonallergic nonsmokers. To date, no studies are available suggesting that this manifestation is due to anything other than the nonspecific irritating effect of cigarette smoke.

Many studies have attempted to assess the relation between tobacco or smoking and asthma. Early investigators, using a variety of skin test materials (*64, 91*), inferred that allergy to tobacco could be causally related to asthma. Subsequent reports have examined the possible role of passive smoking in asthma. Speer (*102*) found that wheezing occurred more frequently in allergic people than in nonallergic people upon exposure to smoke. O'Connell and Logan (*78*), in studying the effects of parental smoking, found that smoke aggravated attacks of asthma in 26 percent of asthmatic children of nonsmoking parents, in contrast to 67 percent of asthmatic children of smoking parents. Importantly, they assessed the effects upon asthmatic children whose parents stopped smoking and reported improvement in 18 of 20 children. In contrast, only 4 of 15 asthmatic children improved when parents continued to smoke. Cameron and coworkers (*15*) concluded that asthmatic children of smoking parents were more often ill with respiratory disease but that this was related to nonspecific irritation rather than hypersensitivity. On the other hand, Rosen and Levy (*92*) published a case report of an infant who developed bronchial asthma associated with exposure to smoke. In this study, reaginic antibody to tobacco extract was documented by passive cutaneous transfer. More conclusive studies that tobacco may be causally related to asthma are reported among tobacco workers. Among 286 persons exposed to raw or fermented tobacco, the incidence of allergic manifestations was 8 percent, of which 17 percent had asthma (*86*). The possible role of tobacco additives has also been considered. Burge, et al. (*13*) reported the occurrence of occupationally-related asthma in a group of 21 industrial workers where colophony or pine resin, a substance also present in cigarettes as adhesives and filter fillings, was implicated.

The consequences of cigarette smoking in the asthmatic patient have also been examined. Townley and coworkers (*112*) reported similar

bronchial airway responses to lung function tests by methacholine inhalation in both smoking and nonsmoking asthmatics. Pimm and associates also reported that passive exposure of asthmatics to cigarette smoke resulted in no consistent significant effect on lung volumes and expiratory flow rates when compared with parallel room air exposure (*84*). On the other hand, Burrows, et al. (*14*), in a study of smoking and tests of lung function, found that an allergic predisposition, asthma or allergic rhinitis, as defined by positive skin reactivity, were associated with an increased susceptibility to bronchoconstrictor effects of cigarette smoking and to recurrent chest infections. That smoking can adversely effect an asthmatic patient in an indirect manner is illustrated by the finding of Powell, et al. (*87*) demonstrating interference with normal metabolism of the bronchodilator agent, theophylline, in smokers.

The concept that hyperreactive airways in asthmatics are due to a regulatory dysfunction of the autonomic nervous system is pertinent to this discussion (*30*). In addition to the effects of specific allergens inducing responsible mediators of bronchoconstriction, it is appreciated that nonspecific irritants (for example odors, temperature extremes, exercise, chemicals) can also act upon the affected cell receptors to precipitate asthmatic attacks.

Thus, apart from any putative allergenic effects of tobacco in a specifically sensitized patient, inhaled tobacco smoke carries the irritant potential to trigger or to aggravate asthmatic symptoms in the patient so affected. Hence, there is further support offered for both cessation of smoking and the following of avoidance procedures of passive exposure in the asthmatic individual.

Allergic effects of tobacco on the cardiovascular system have also received considerable attention. It is well documented that cardiac abnormalities occur in association with allergic phenomena, for example, anaphylaxis or allergic shock (*5*, *25*, *73*). However, whether tobacco may play a role in cardiovascular alterations apart from known pharmacologic effects is still not clear. Harkavy's series of observations (*36*, *37*, *38*, *39*, *40*, *42*, *43*) would support the concept that allergy to tobacco leaf may have important implications in a variety of cardiac and vascular diseases. In these he would include cardiac arrythmias, intensification of coronary artery insufficiency, thromboangiitis obliterans, migrating phlebitis, and some forms of allergic vasculitis. Although acknowledging the pharmacologic effects of nicotine on the cardiovascular system, Harkavy also suggests that it may act as a hapten in inducing allergic responses. Recent observations by Becker and coworkers (*10*), using a partially characterized antigenic component of tobacco, led them to hypothesize that circulating tobacco antigens in sensitive individuals might react with corresponding antibody to produce focal injury of blood vessels. If this hypothesis is corroborated, design of further studies of potential adverse conse-

quences of possible tobacco allergy on the cardiovascular system will be possible.

That tobacco may operate through the mechanism of cell-mediated immunity or delayed hypersensitivity is suggested by case reports of contact dermatitis caused by tobacco smoke and tobacco smoke residue (*19, 24, 122*). Recent surveys among tobacco workers have shown that contact dermatitis related to tobacco was responsible for 14 percent of skin eruptions occurring in this industrial sample (*3*). By contrast, however, an earlier survey (*96*) could not implicate tobacco as a cause of dermatitis among cigar factory workers. It has been pointed out that dermatitis among tobacco workers probably represents a nonspecific response due to injury, moisture, or irritants, especially those from the chemicals or other fertilizers used in the growing process (*122*). To date, therefore, there is little evidence that allergic skin manifestations due to tobacco occur with any significant frequency.

Summary

1. Tobacco and tobacco smoke extracts have been found to act as antigens inducing both precipitating and reaginic antibodies in experimental animals. Tobacco leaf products can also sensitize lymphocytes participating in cell-mediated immune functions.

2. Tobacco and its combustion products are known to be heterogeneous mixtures of particulate and gasous materials. Additionally, natural contaminants and intentional additives increase the array of components, presenting a complex of toxic, pharmacologic, irritant, and inflammatory effects that can complicate interpretation of a precisely defined role for tobacco in immune and allergic processes.

3. Several tobacco antigens have been isolated by chemical procedures. Of special interest is a glycoprotein common to both tobacco extracts and smoke antigenically corresponding with reaginic antibody in humans.

4. Epidemiologic samplings to define the presence of true allergy to tobacco, either among healthy persons or among those suffering from known allergic conditions, are inconclusive.

5. Tobacco smoking exerts a variety of effects on respiratory tract structures involved in local host defense, and chronic smoking leads to consistent histological changes in the respiratory tract.

(a) There is evidence to indicate an adverse effect of long-term smoking on the mucociliary transport mechanisms and mucus composition.

(b) The number of macrophages isolated from lung fluids of smokers is increased over nonsmokers.

(c) Changes in the ultrastructure of macrophages—most notably the presence of cytoplasmic inclusions—are found in smokers.

(d) Alveolar macrophages from smokers have altered metabolism and measurable degrees of physiologic impairment.

6. Alterations of indicators of humoral immunity have been demonstrated in the respiratory tracts of smokers, and smoking may impair systemic humoral immunity both *in vitro* and *in vivo*.

7. Alterations in assays of cell-mediated immunity are noted locally and systemically in smokers.

8. Leukocytosis and reversible hypereosinophilia have been seen in smokers.

9. The ability to make a definitive diagnosis of tobacco allergy is complicated by the difficulty of demonstrating a cause and effect relationship between immunologic events and disease manifestations; additional evidence is required to establish whether there is a definitive role for tobacco smoke sensitization in causing allergic diseases.

10. Studies concerned with the adverse consequences of either active or passive smoking have shown that allergic individuals, especially those with rhinitis or asthma, may, in fact, be more sensitive to the nonspecific noxious effects of cigarette smoke than healthy individuals.

Conclusion and Comment

Apart from symptom-relieving drugs, there are no known effective therapeutic measures to prevent or combat the adverse effects of smoking on immune function and on allergy-related problems. It is evident that further studies defining tobacco antigens, determining the clinical incidence of tobacco allergy, further clarifying the nature of immune responses to tobacco, and improving the diagnostic agents and materials should be undertaken. Such studies, however, can not be expected to have an impact on improving the health of individuals subject to tobacco's adverse effects comparable to that which would result from adhering to the mainstay of management of the allergic patient—complete avoidance of the incriminated substance.

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11. INVOLUNTARY SMOKING.

CONTENTS

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Introduction

The effects of smoking on the smoker have been extensively documented in other chapters of this report. This chapter will review the effects of tobacco smoke on the nonsmoker, an area in which there has been increasing concern in the past several years (*66a, 76, 77*). This topic has been referred to as "passive smoking" or "secondhand" smoking as well as "involuntary smoking." The term involuntary smoking will be used to mean the inhalation by the nonsmoker of tobacco combustion products from smoke-filled atmospheres. This type of exposure is, in a sense, "smoking" because it provides exposure to many of the same constituents of tobacco smoke that voluntary smokers experience. It is also "involuntary" because the exposure occurs as an unavoidable consequence of breathing in a smoke-filled environment.

The chemical constituents found in an atmosphere filled with tobacco smoke are derived from two sources—mainstream and sidestream smoke. Mainstream smoke emerges from the tobacco product while being drawn through the tobacco during puffing. Sidestream smoke rises from the burning cone of tobacco. For several reasons, mainstream and sidestream smoke contribute different concentrations of many substances to the atmosphere: different amounts of tobacco are consumed in the production of mainstream and sidestream smoke; the temperature of combustion for tobacco is different during puffing than while smouldering; and certain substances are partially absorbed from the mainstream smoke by the smoker. The amount of a substance absorbed by the smoker depends on the characteristics of the substance and the depth of inhalation by the smoker.

When the smoker does not inhale the smoke into his lungs, the smoke he exhales contains less than half its original amount of water-soluble volatile compounds, four-fifths of the original nonwater-soluble compounds and particulate matter, and almost all of the carbon monoxide (*25*). When the smoker inhales the mainstream smoke, he exhales into the atmosphere less than one-seventh of the amount of volatile and particulate substances that were originally present in the smoke, and he also reduces the exhaled CO to less than half its original concentration (*26*). As a result, different concentrations of substances are found in exhaled mainstream smoke depending on the tobacco product, composition of the tobacco, and degree of inhalation by the smoker.

The effects of cigarette smoke on the environment and on the nonsmoker in the environment will be examined by reviewing data on the constituents of cigarette smoke measured under various conditions and on the absorption of these constituents by the nonsmoker. The physiologic effects of this "involuntary smoking" will then be considered.

Constituents of Tobacco Smoke and Their Absorption by the Nonsmoker

Brunnemann, et al. (*14*) have recently presented a compilation of the levels of some of the important substances in mainstream cigarette smoke and the ratio of sidestream to mainstream levels for these substances (Table 1). The actual amount of the substance and the mainstream-to-sidestream ratio will vary with different types of tobacco tested and the method used to burn the cigarette, but Table 1 gives values generally consistent with those found by others (*23*, *45*, *50*). Many of the substances, including nicotine, carbon monoxide, and ammonia, are found in much higher concentrations in sidestream smoke than in mainstream smoke. Thus, the total smoke exposure of nonsmokers is quantitatively much smaller than the exposure of smokers, but the smoke nonsmokers inhale may be qualitatively richer in certain compounds than mainstream smoke. This qualitative

TABLE 1.—Constituents of Cigarette Smoke.[1] Ratio of sidestream smoke (SS) to mainstream smoke (MS)

A. GAS PHASE	MS	SS/MS		MS	SS/MS
Carbon Dioxide	20–60 mg	8.1	Nitrogen Oxides (NO_x)		
Carbon Monoxide	10–20 mg	2.5	Ammonia	80 μg	73
Methane	1.3 mg	3.1	Hydrogen cyanide	430 μg	0.2
Acetylene	27 μg	0.8	Acetonitrile	120 μg	3.9
Propane Propene	0.5 mg	4.1	Pyridine	32 μg	10
Methylchloride	0.65 mg	2.1	3-Picoline	24 μg	13
Methylfuran	20 μg	3.4	3-Vinylpyridine	23 μg	28
Propionaldehyde	40 μg	2.4	Dimethylnitrosamine	10–65 μg	52
2-Butanone	80–250 μg	2.9	Nitrospyrrolidine	10–35 μg	27
Acetone	100–600 μg				

B. PARTICULATE PHASE	MS	SS/MS		MS	SS/M
"Tar"	1–40 mg	1.7	Quinoline	1.7 μg	11
Water	1–4 mg	2.4	Methylquinolines	0.7 μg	11
Toluene	108 μg	5.6	Aniline	360 ng	30
Stigmasterol	53 μg	0.8	2-Naphthylamine	2 ng	39
Total Phytosterols	130 μg	0.8	4-Aminobiphenyl	5 ng	31
Phenol	20–150 μg	2.6	Hydrazine	32 ng	3
Catechol	130–280 μg	0.7	N'-Nitrosonornicotine	100–500 ng	5
Napthalene	2.8 μg	16	NNK[2]	80–220 ng	10
Methylnaphthalene	2.2 μg	28	Nicotine	1–2.5 mg	2
Pyrene	50–200 μg	3.6			
Benzo(*a*)pyrene	20–40 μg	3.4			

[1]Nonfilter cigarette
[2]NNK = 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (tobacco specific carcinogenic nitrosamine)
SOURCE: Adapted from Brunnemann (*14*).

TABLE 2.—Measurement of constituents of tobacco smoke in experimental conditions.[1]

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	Measure of absorption
Anderson and Dalhamn (*3*).				
Room 80 m^3	6.4 air changes per hour	46 cig & 3 pipefuls	4.5 ppm CO 377 mg/m^3 nicotine	COHb .6%
Bridge and Corn (*13*).				
Party room 145 m^3	7.0 air changes per hour	50 cig & 17 cigars in 1.5 hr	7.0 ppm CO	
Party room 101 m^3	10.6 air changes per hour	63 cig & 10 cigars in 1.5 hr	9.0 ppm CO	
Brunnemann, et al. (*16*).				
Box .4 m^3	none	10 cig in 1 hr	2.7 ng/l dimethylnitrosamine	
	1.5 liters/min	10 cig in 1 hr	2.9 ng/l dimethylnitrosamine	
Small room 20 m^3	none	100 cig in 1 hr	.33 ng/l dimethylnitrosamine	
	none	100 cig in 1 hr	.23 ng/l dimethylnitrosamine	
	some	100 cig in 1 hr	1.85 ng/l dimethylnitrosamine	