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INTRODUCTION

As early as 1886 reference was made to an entity called "tobacco asthma" (*64*). Subsequently, controversy has arisen over whether tobacco smoking causes clinical allergy (*61*) and whether such tobacco allergy is associated with the major smoking-related diseases (*25, 69*).

In 1957, Silvette, et al. (*64*) reviewed more than 100 papers concerned with "the immunological aspects of tobacco and smoking." They concluded that inadequate animal studies had been performed in this area. Referring to clinical studies, they observed: "... virtually all reported clinical investigation has been limited to determinations of cutaneous sensitivity to tobacco extracts; and it must be regretfully admitted that much of this published work is equivocal, uncritical, and inadequately controlled."

Such criticism is also applicable to many studies published since then.

Epidemiologic studies designed to determine the prevalence of tobacco allergy have not been carried out; hence, it is difficult to evaluate the magnitude of the problem.

Allergy may be defined as a specific alteration in response mediated by an antigen-antibody reaction. When a hereditary susceptibility to allergic illness is present, the term atopy is used. For example, hay fever and asthma are atopic diseases.

There is no single test or observation which can be used to determine whether a substance may be responsible for allergic disease; however, fulfillment of the following criteria constitutes evidence for such a relationship:

1. Demonstration that the substance is antigenic, i.e., capable of stimulating the production of antibody and then reacting with the antibody.
2. Demonstration that, upon exposure to the substance, signs and symptoms simulating an allergic reaction are elicited which disappear upon its removal.
3. Demonstration that the immunologic event is related to the clinical event.

Recent advances in the understanding of immunological reactions as well as in the methodology of immunology are now being applied

to problems of clinical allergy. For example, Ishizaka (*37*), using radioimmunoelectrophoresis, recently reported that the so-called "allergic antibody" (reagin, skin-sensitizing antibody (SSA), atopic antibody) belongs to a new class of immunoglobulins, IgE.

Although the skin test remains a simple and definitive method of demonstrating reagins in the allergic patient, there are many variables involved in this technique which must be carefully weighed when interpreting test results. In the area of tobacco skin testing, such variables include: differences in antigenic content of the test extract, differences in route of administration, and heterogeneity of test groups.

ANTIGENIC PROPERTIES

Tobacco leaf contains a complex mixture of chemical components including: celluloses, starches, proteins, sugars, alkaloids, pectic substances, hydrocarbons, phenols, fatty acids, isoprenoids, sterols, and inorganic minerals (*69*). Theoretically, relatively few of these substances should be antigenic. Tobacco extracts of different composition result from differences in tobacco types and species, processing of tobacco, and preparation of the extract. Harkavy (*26*) has shown in some patients a differential skin reactivity to extracts from different types of tobacco. Coltoiu, et al. (*9*) reported that 13 different antigens capable of inducing precipitins in rabbits have been isolated from tobacco pollen. Chu, et al. (*7*) prepared aqueous extracts of five commercial tobacco products which stimulated antibody formation in rabbits. The antigens contained in the extracts included both proteins and polysaccharides and had molecular weights ranging from 20,000 to 60,000.

Silvette, et al. (*64*) reviewed several papers dealing with the immunology of nicotine and concluded that nicotine was nonantigenic. Harkavy (*25*), who performed some of the earliest studies on the antigenicity of nicotine, could not exclude the possibility that nicotine may act as a hapten. A hapten is a compound which, although not antigenic by itself, reacts with antibody and conveys antigenic specificity when combined with another compound.

With pyrolysis many of the tobacco constituents undergo reactions involving oxidation, dehydrogenation, cracking, rearrangement, and condensation (*69*). Many new compounds are formed. Pipes (*51*) demonstrated, through exhaustion of passive transfer reactivity in skin sites, that allergy to tobacco smoke in man is distinct from that of allergy to tobacco leaf. Tobacco smoke exhausted reactivity in sites injected with tobacco smoke sensitized serum; reactivity was reduced but not exhausted with tobacco extract. The converse was true with passive transfer sites of tobacco-sensitized serum; tobacco extracts abolished allergic reactivity whereas to-

bacco smoke extract produced a diminution but not total exhaustion. He concluded that it would be useful to test human subjects for both tobacco leaf and tobacco smoke sensitivity. Kreis, et al. (*39*) have speculated that tobacco leaf antigenicity may be lost with pyrolysis.

Coltoiu, et al. (*9*) recently emphasized the importance of removing all irritants from test extracts. In a clinical setting, allergy to tobacco additives such as menthol has also been suspected (*47*).

SKIN TESTING

Intracutaneous injection of test antigen is a widely used method of skin testing. Patch tests have also been used in cases of suspected contact dermatitis.

Rosen (*54*) has observed that skin testing does not accurately duplicate the most common route of exposure to tobacco, i.e., tobacco smoke inhalation. For those involved in the production of tobacco products, inhalation of tobacco dust or direct contact with tobacco may play important roles in sensitization (*9*).

The extensive literature on cutaneous sensitivity to tobacco extracts includes comparisons of the prevalence of positive skin reactions in different groups, such as "normal" nonsmoking adults (*17, 68*), "normal" smokers (*17, 33*), allergic patients (*59, 76*), children (*41, 50*), tobacco workers (*6, 9*), and patients with specific diseases, e.g., thromboangiitis obliterans (*28, 73*). Harkavy reported on tobacco skin reactions in several different groups of patients (*30*). Many of the apparently discordant results in some of these reports can be traced to failure to compare similar populations or to control for differences in the test antigen or in the method of testing.

Sulzberger (*66*) studied the different types of skin reactions produced by intracutaneous injection of denicotinized tobacco extract. Three types of positive skin responses were observed: eczematous reactions; immediate wheal-and-flare reactions; and late reactions, probably of the tuberculin type. The wheal-and-flare response has been by far the predominant type (*42*).

This immediate wheal-and-flare response is a specific immune reaction (*64*) largely mediated by IgE. Patterson (*48*) recently proposed a simplified model explaining the mechanism of action of the skin sensitizing antibody (SSA). "Subsequent to stimulation of the animal by antigen, SSA are produced by cells of the lymphoid system possibly located in the alimentary and respiratory tract.... The SSA so produced are secreted in such a way that they reach the circulation, where circulating cells, predominantly basophilic leukocytes, are sensitized by attachment of the SSA to the cell surface. In addition, the SSA also leave the vascular compartment and sensitize mediator-releasing cells in tissues. The tissue cells are primarily mast cells... The immediate-type allergic reaction occurs

when antigen is introduced into the individual sensitized by SSA, either by transfer of antigenic molecules through the respiratory or alimentary mucosal surface or by injection into the skin or vascular system. The antigens reach the antibody on the surface of the mast cells and initiate the intracellular events that result in mediator release from the cells." The actions of these mediators include smooth muscle contraction, vasodilation, and increased capillary permeability which can produce such clinical pictures as hay fever, asthma, and generalized anaphylaxis.

Until recently, direct skin testing and the passive transfer test (Prausnitz-Küstner reaction) were the only methods of studying IgE mediated responses. In the passive transfer test, serum from an allergic patient is injected into the skin of a normal subject. After a suitable interval the antigen is injected into the prepared site and adjacent normal skin. In a positive response, cutaneous reactivity is transferred to the normal subject at the injection site. The absence of a positive response in nearby normal skin excludes nonspecific irritation as a cause of the response and shows that the normal subject is not himself allergic to the antigen.

Harkavy and Witebsky (*34*) found and selectively absorbed tobacco reagins in patients showing multiple sensitivities. This selective absorption documented the immunologic mechanism of the skin reaction. Passive transfer of the SSA was also reported by Peshkin and Landay (*50*) and by Lima and Rocha (*41*). Lowell (*43*) stated, "The individual possessing skin-sensitizing antibody to the tobacco extract may be regarded as unequivocally allergic to the extract...." Despite the inability of Sulzberger and Feit (*67*) to demonstrate tobacco reagins in their skin test positive patients, several investigators have found them (*26, 50, 75*).

Harkavy (*23*) biopsied urticarial wheals after intradermal injection of tobacco extract and found a local eosinophilia. He felt that this helped confirm the allergic mechanism of the positive skin test. He also biopsied the site of a delayed skin reaction to tobacco and found an eczematous type of response.

The delayed type hypersensitivity reaction is manifested by induration and erythema developing within 24 to 48 hours after injection of antigen. The absence of response in the first 6 to 8 hours after exposure to antigen helps exclude an Arthus reaction, which is also a slowly evolving allergic response. Serum antibodies are not involved in the initiation of delayed type hypersensitivity; rather, the initial step is thought to involve interaction of antigen and specialized lymphocytes (*10, 11*). Contact dermatitis is thought to be very nearly a pure type, delayed hypersensitivity reaction (*10, 11*).

The foregoing discussion has highlighted the studies concerning cutaneous sensitivity to tobacco extracts. Despite the complexities and contradictions, numerous workers agree that tobacco extract

(leaf or smoke) is antigenic and can sensitize (*2, 7, 9, 18, 26, 43, 50, 52, 64, 66, 76*). Silvette, et al. (*64*) concluded, "It is, indeed, beyond question that allergy to tobacco extracts, presumably atopic in nature, is an established fact. . . ."

Lowell (*43*) observed that, in most instances, skin reactivity to an extract of tobacco actually means the presence of allergy in some degree to something in the extract. Armen and Cohen (*2*), Harkavy and Perlman (*31*), and Popescu, et al. (*52*) observed that tobacco extract is weakly antigenic. Armen and Cohen (*2*) were able to sensitize rabbits to tobacco proteins only after absorbing the protein to aluminum hydroxide, which served as an adjuvant.

Even though a positive skin test to tobacco extract may be due to a specific allergic reaction, the interpretation of such a positive test in a given patient or group of patients poses problems, since sensitivity to a battery of antigens has been demonstrated in individuals who are entirely free from allergic symptoms upon exposure to the antigens. Rosen (*54*) stated that this lack of correlation between positive skin tests and clinical symptoms is greater for tobacco than for other antigens such as pollens, dusts, and feathers. He and others have emphasized that the skin test has value only when correlated with clinical evidence.

Analysis of skin test studies in nonsmokers (*64*) shows that approximately 15 percent of such "healthy" individuals give positive reactions to tobacco extracts. Some studies of smokers reporting a 30 percent or more prevalence of skin sensitivity to tobacco extract (*33, 43*) have considered patients with multiple sensitivities, including that to tobacco. Atopic individuals have been noted to have a greater prevalence of skin sensitivity to tobacco than nonatopics (*64*); hence, in some studies an excess of atopic patients may account for a substantial part of the elevated prevalence of tobacco skin sensitivity reported for smokers.

Several workers have sought to use the skin test as a screening device for indicating an unusual susceptibility to the adverse effects of tobacco. DeCrinis, et al. (*13*), Fontana (*17*), and Redisch (*53*) have reported that patients with positive skin tests to tobacco extracts were more likely to have an adverse vascular response to tobacco as indicated by a fall in peripheral skin temperature on smoking. More recent studies have shown that a decrease in skin temperature with smoking is a reproducible response to nicotine found in "normal" individuals and does not appear to be confined to a specific group of smokers (*1, 56, 70*).

ADDITIONAL IMMUNOLOGICAL EFFECTS

Additional evidence is available to support the view that tobacco induces immunologic changes in man and animals. Armen and

Cohen (*2*), Chu, et al. (*7*), Harkavy and Perlman (*31*), and Zussman (*76*) induced precipitin formation in animals sensitized to tobacco extract. Kreis, et al. (*39*) studied precipitation reactions in 651 hospitalized patients, many of whom were suffering from tuberculosis or lung cancer. A precipitation reaction between the patients' sera and a commercial tobacco extract was found in 62.5 percent of the patients. Chu, et al. (*7*), using the same antigens as those employed to stimulate precipitin formation in rabbits, found serum antibodies in 40 percent of a group of smokers which precipitated specificially with the tobacco antigens. Only 7 percent of a group of nonsmokers demonstrated these antibodies.

Savel (*59*) studied eight nonsmoking, allergic individuals who developed immediate upper respiratory discomfort after being exposed to cigarette smoke. As measured by the uptake of tritiated thymidine, the lymphocytes of these individuals were stimulated by cigarette smoke, while "normal" lymphocytes were depressed. The author stated that the correlation of this test with specific forms of clinical allergy remains uncertain.

Some investigators have observed abnormal laboratory test results in smokers as compared to nonsmokers, which may indicate an allergic response in the former group. Schoen and Pizer (*60*) described a smoking woman who demonstrated a striking blood eosinophilia while smoking cigarettes. Upon cessation of smoking, the eosinophil count returned promptly to normal levels. Resumption of smoking was associated with a return of the eosinophilia. Heiskell, et al. (*36*) found a significant increase in C-reactive protein and an abnormal seroflocculant for ethyl choledienate in smokers as compared to nonsmokers. Plasma histaminase levels were reported by Kameswaran, et al. (*38*) to be elevated in smokers.

Experimental animal sensitization to tobacco was reported by Friedlander, et al. (*19*) in male rats. Harkavy (*29*) confirmed these results in male rats and also obtained positive Schultz-Dale reactions in the sensitized animals; however, female rats failed to demonstrate this sensitization. Harkavy (*24*) reported cardiac histological abnormalities in three rabbits sensitized with denicotinized tobacco extracts. The abnormalities found in the three rabbits, respectively, included: intimal proliferation, focal fragmentation of the internal elastic membrane, and loss of smooth muscle fibers in the media of a branch of a coronary artery; focal intimal proliferation and fibrinoid alterations in the media of a small coronary vessel; and a focus of myocardial fibrosis and necrosis.

EFFECT ON THE IMMUNE RESPONSE

The effect of tobacco on the immune response has received some attention. Early studies in rabbits suggested that tobacco smoke re-

tarded the production of agglutinins in rabbits immunized against typhoid (*14*).

A variety of observations indicate that ingestion of antigenic material by the macrophage may be an essential step in the immune response (*3*). Bruni (*5*) found that cigarette smoke suppressed phagocytosis in rabbits. Green and Carolin (*20*) performed *in vitro* studies in rabbit alveolar macrophages and observed that cigarette smoke inhibited the capacity of these cells to inactivate bacteria. Harris, et al. (*35*) reported no differences in the phagocytic ability of macrophages taken from human smokers and nonsmokers, but he also concluded that his data neither contradicted nor supported Green's work. Cohen and Cline (*8*), while noting that macrophages from smokers had normal phagocytic capacity, demonstrated suboptimal macrophage function in an environment of low O_2 tension, a state found more frequently in smokers than nonsmokers. Maxwell, et al. (*45*), using guinea pigs, found that smoke exerted no effect on phagocytosis; nevertheless, smoke seemed to impair the phagocytes' ability to inactivate bacteria. Nicotine has been shown by Meyer, et al. (*46*) to exert a depressant effect on sheep pulmonary alveolar macrophage respiration and ATPase activity. Recently, Yeager (*74*) reported that water soluble constituents of cigarette smoke depress protein-synthesis in rabbit alveolar macrophages *in vitro*.

Lewis, et al. (*40*) found that cigarette smoking had a suppressive action on secretory IgA production in normal subjects but not in subjects with chronic respiratory disorders. Vos-Brat and Rumke (*71*) recently reported that IgG serum concentrations and the response of lymphocytes to phytohemagglutinin were significantly lower in smokers than nonsmokers.

A number of investigators have reported increased rates of respiratory illnesses among cigarette smokers (*70*). Finklea, et al. (*16*) studied antibody response in 289 volunteers after the 1968 Hong Kong influenza epidemic. They reported a significant decrease among cigarette smokers in the persistence of hemagglutination inhibition antibody after natural infection or vaccination with A_2 antigens. They postulated that this antibody deficit among cigarette smokers might be related to increased illness during influenza outbreaks.

IRRITANT AND PHARMACOLOGIC EFFECTS

As Lowell (*43*) has emphasized, the pharmacologic, irritant, and allergic effects of tobacco are difficult to distinguish. Acrolein and acetaldehyde are potent irritants found in tobacco smoke, which, as demonstrated in animal studies, are capable of releasing chemical mediators such as histamine (*58*). The inhalation of tobacco smoke

causes bronchial constriction, mucus hypersecretion, and ciliary stasis (*57*) in man, all of which can contribute to a clinical picture indistinguishable from an allergic reaction. Several authors (*44, 61, 63*) share Sherman's (*62*) view that "... tobacco smoke is an important secondary factor in precipitating allergic symptoms through its action as a nonspecific irritant."

Speer (*65*) recently compared the subjective responses of two groups of nonsmokers to tobacco smoke exposure. One group of 191 patients suffered from documented allergies. In one-sixth of these patients a positive skin test to tobacco extract was found, but only a few patients were seen with objective symptoms which could be traced to tobacco smoke. The other group of 250 patients had no history of allergy and was studied by questionnaire only. Eye irritation, nasal symptoms, headache, and cough were common in both groups. Speer concluded that these effects of tobacco smoke were irritative rather than allergic in origin. The data presented in this study demonstrate that tobacco smoke can contribute to the discomfort of many individuals; they do not rule out a possible contribution from allergic reactions.

Harkavy (*30*) cited experimental data distinguishing allergic effects from pharmacologic effects of smoking such as increased heart rate and decreased skin temperature.

Additional studies are needed to separate the pharmacologic, irritant, and allergic effects of tobacco smoke.

CLINICAL ALLERGY

It is important to understand what role tobacco and tobacco smoke may play in clinical allergy because many individuals are exposed to them in varying concentrations throughout the year.

A variety of conditions have been ascribed to allergic manifestations toward tobacco leaf or smoke including: asthma, rhinitis, urticaria, angioneurotic edema (giant hives), contact dermatitis, migraine headache, gastrointestinal symptoms, and various cardiovascular disturbances (*64*); however, some case reports are lacking in documentation (*4, 49*). A small group of patients having cutaneous sensitivity to tobacco and showing complete disappearance of symptoms when free from exposure to tobacco were reported by Rosen and Levy (*55*). Included in this group were cases of asthma and urticaria.

Studies of atopic individuals have revealed a group of nonsmoking patients with cutaneous sensitivity to tobacco who developed clinical symptoms upon exposure to tobacco smoke (*59, 76*). In none of these studies (*54, 59, 76*) have detailed immunologic investigations, attempting to link clinical and immunologic events, been performed.

Lowell (*43*) reviewed case reports of contact dermatitis to to-

bacco among tobacco workers and noted that because of "...the small proportion of exposed individuals who develop such lesions, and the tendency for it to clear completely when contact with tobacco is avoided and to return on reexposure, an allergic cause in certain instances would appear to be highly probable." Recently, case reports have appeared identifying tobacco smoke and tobacco smoke residue as causes of contact dermatitis (*6, 12, 72*).

Harkavy's (*28*) early reports of a greater number of reactors to tobacco extract among patients with thromboangiitis obliterans (TAO) than among controls drew attention to the cardiovascular system as a possible "susceptible" organ for allergic reactions (*15*). Harkavy continues to be a strong proponent of the role of tobacco allergy in a wide range of cardiovascular abnormalities, including coronary artery disease (*21, 22, 25, 27, 31, 32*). This view on tobacco allergy as one of the etiological factors in coronary heart disease (CHD) has not received much attention.

Silvette, et al. (*64*) reviewed reports (*28, 33, 66, 68, 73*) on the prevalence of skin sensitivity in patients with TAO as compared to controls and cited possible reasons for a higher prevalence of positive skin tests to tobacco in these patients.

In general, the evidence relating TAO to tobacco allergy is inconclusive.

SUMMARY

1. Tobacco leaf, tobacco pollen, and tobacco smoke are antigenic in man and animals.
2. (a) Skin sensitizing antibodies specific for tobacco antigens have been found frequently in smokers and nonsmokers. They appear to occur more often in allergic individuals. Precipitating antibodies specific for tobacco antigens have also been found in both smokers and nonsmokers.
   (b) A delayed type of hypersensitivity to tobacco has been demonstrated in man.
   (c) Tobacco may exert an adverse effect on protective mechanisms of the immune system in man and animals.
3. (a) Tobacco smoke can contribute to the discomfort of many individuals. It exerts complex pharmacologic, irritative, and allergic effects, the clinical manifestations of which may be indistinguishable from one another.
   (b) Exposure to tobacco smoke may produce exacerbation of allergic symptoms in nonsmokers who are suffering from allergies of diverse causes.
4. Little is known about the pathogenesis of tobacco allergy and its possible relationship to other smoking-related diseases.

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CHAPTER 8

Public Exposure to Air Pollution From Tobacco Smoke

Contents

LIST OF TABLES

PUBLIC EXPOSURE TO AIR POLLUTION FROM TOBACCO SMOKE

The purpose of this chapter is to summarize the present state of evidence concerning the effects of exposure to an atmosphere containing either tobacco smoke or its constituents. Since the identification of cigarette smoking as a serious health hazard to the smoker was based on clinical and epidemiological observations that nonsmokers have much lower mortality and morbidity rates from a number of conditions, it is obvious that cigarette smoking is normally a greater hazard to the smoker than is the typical level of exposure to air pollutants produced by the smoking of cigarettes which many nonsmokers experience. This would be consistent with the voluminous data which show a dose-response relationship between the level of exposure to smoke and the magnitude of its effect.

The research so far reported on the nature and effects of exposure to smoke-pollutants in the atmosphere has not been as extensive and well-controlled as that done on the health effects of smoking on the smoker himself. Knowledge on this subject can be separated into four major areas of concern:

1. The extent to which the components of cigarette smoke contaminate the atmosphere and are absorbed by the nonsmoker.
2. The effects of low levels of carbon monoxide on human health.
3. Allergic, adverse, and irritative reactions to cigarette smoke among nonsmokers.
4. The known harmful effects of the passive inhalation of cigarette smoke in animals.

THE EXTENT TO WHICH THE COMPONENTS OF CIGARETTE SMOKE CONTAMINATE THE ATMOSPHERE AND ARE ABSORBED BY THE NONSMOKER

Theoretical models of this contamination have been constructed. Owens and Rossano (*44*) have noted that most popular cigarettes release into the atmosphere approximately 70 mg. of dry particulate matter (about 60 mg. in the sidestream and slightly over 20 mg. in the mainstream, about one-half of the latter being absorbed by the smoker and one-half expelled into the ambient air) and 23 mg. car-

bon monoxide per cigarette. This material adds to the cleaning problem of the air of any enclosed space and contributes to residual odors. In a recent study of particulate matter filtration in domestic premises (*35*), the authors observed that the smoking of one cigar completely overcame the effect of an electrostatic filtration device for one hour.

Atmospheric pollutants caused by smoking are derived from two major sources: mainstream and sidestream smoke. Mainstream smoke emerges from the tobacco product through the mouthpiece during puffing, whereas sidestream smoke comes from the burning cone and from the mouthpiece during puff intermissions (*60*). The tobacco smoke released into the atmosphere consists of all the sidestream smoke as well as that part of the mainstream smoke which has been either held in the smoker's mouth or taken into his lungs and then expelled. The actual amount of material to which individuals are exposed in the presence of smokers depends upon the amount of smoke produced, the depth of inhalation on the part of the smoker, the ventilation available for the removal or dispersion of the smoke, and the proximity of the individual to the smoker. The length of time of exposure to those pollutants is extremely important in determining how much is absorbed into the body. The pattern of smoking influences the amount produced by altering the content of the exhaled smoke. As shown by Dalhamn, et al. (*10, 11*), mouth absorption removes approximately 60 percent of the water-soluble volatile components (e.g., acetaldehyde), 20 percent of the nonwater-soluble volatile components (e.g., isoprene), 16 percent of the particulate matter, and only three percent of the carbon monoxide. Thus, the smoker who does not inhale "filters" a portion of the smoke components in his mouth before expelling them into the ambient air. On the other hand, the lungs retain from 86 to 99 percent of the volatile and particulate substances and approximately 54 percent of the carbon monoxide inhaled. Hence, the inhaling smoker "filters" the mainstream smoke rather effectively before expelling it into the ambient air. A factor which has apparently not been investigated is the difference in the smokers' "filtration" of mainstream smoke when the smoke is exhaled through the nose instead of the mouth.

Thus, the nonsmoker breathes smoke-containing air composed of sidestream smoke and mainstream smoke exhaled by smokers. The inhaling smoker receives nearly the full amount of mainstream smoke as well as a portion of sidestream smoke and smoke exhaled by himself and other smokers. The smoker who does not inhale receives those compounds which are absorbed from the mainstream smoke in his mouth, as well as absorbing the sidestream smoke and the smoke exhaled by himself and other smokers contained in the air he breathes.

Since pipe and cigar smokers inhale less commonly than do cigarette smokers, their contribution to the substances in the air breathed in exposure to smoke pollutants consists of a composite of sidestream smoke and relatively unfiltered mainstream smoke which has been held in the mouth and then expelled.

The actual effluents in the mainstream and sidestream cigarette smoke have been considered by Pascasio, et al. (*45*) and Scassellati Sforzolini and colleagues (*50, 51*). These authors stated that "tar" and nicotine levels in sidestream smoke may be significantly higher than those of mainstream smoke and may be harmful to the nonsmoker. Actual volume measurements were not reported, however.

Actual measurements of the contamination due to cigarette smoking have been carried out by a number of research groups. A recent, well-controlled study by Harke (*24*) involved the smoking of 42 cigarettes in 16 to 18 minutes using German blend cigarettes of 85 mm. length, 18 mm. filter, and smoked to a 25 mm. butt length in a room with a volume of 57 cubic meters (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 12 by 14 feet). The author observed that in the absence of ventilation the atmosphere contained up to 50 p.p.m. carbon monoxide and .57 mg./m.^{3} nicotine. With substantial ventilation, these levels fell significantly (to approximately 10 p.p.m. carbon monoxide and .10 mg./m.^{3} nicotine). He also found that cigar smoke (9 cigars of Clear Sumatra tobacco smoked in 30 to 35 minutes) produced similar amounts of contamination while pipe smoke (3 grams of Navy type medium cut tobacco smoked as eight pipefuls in 35 to 40 minutes) produced much less. Other authors have made similar measurements. Galuskinova (*20*) found that 3,4-benzpyrene levels in a smoky restaurant were from 2.82 to 14.4 mg./100 m.^{3} as compared to outside atmospheric levels of 0.28 to 0.46 mg./100 m.^{3}, although burning of food particles may have contributed to the presence of 3,4-benzpyrene in this setting. Kotin and Falk (*33*) have shown that sidestream cigarette smoke condensate may contain more than three times as much benzo(a)pyrene as mainstream smoke. Srch (*55*) observed that the smoking of 10 cigarettes to a 5 mm. butt length in an enclosed car of 2.09 m.^{3} volume produced carbon monoxide levels up to 90 p.p.m. Lawther and Commins (*34*), working with a ventilated chamber, found levels of up to 20 p.p.m. of carbon monoxide after seven cigarettes were smoked in one hour; however, peaks of up to 90 p.p.m. were recorded at the seat next to the smoker. Coburn, et al. (*9*) recorded levels of 20 p.p.m. of carbon monoxide in a small conference room after 10 cigarettes were "burned." Harmsen and Effenberger (*25*) reported up to 80 p.p.m. of carbon monoxide in an enclosed 98 m.^{3} room (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 18 by 20 feet) in which 62 cigarettes had been smoked in two hours.

TABLE 1.—*Percent of COHb during and following exposure to 50 p.p.m. of CO.*

Time during exposure	Mean	Range	Number of subjects
Preexposure	0.7	0.4–1.5	11
30 minutes	1.3	1.3	3
1 hour	2.1	1.9–2.7	11
3 hours	3.8	3.6–4.2	10
6 hours	5.1	4.9–5.5	5
8 hours	5.9	5.4–6.2	5
12 hours	7.0	6.5–7.9	3
15 ½ hours	7.6	7.2–8.2	3
22 hours	8.5	8.1–8.7	3
24 hours	7.9	7.6–8.2	3
Time without exposure after 1 hour of exposure			
30 minutes	1.8	1.8	3
1 hour	1.7	1.6–1.8	3
2 hours	1.5	1.4–1.5	3
5 hours	1.1	1.0–1.1	2
Time without exposure after 3 hours of exposure			
30 minutes	3.7	3.4–3.9	3
1 hour	3.3	2.7–3.8	3
2 hours	2.7	2.3–3.0	3
Time without exposure after 8 hours of exposure			
30 minutes	5.6	5.1–5.9	3
1 hour	5.1	4.8–5.4	3
1 ¾ hours	4.0	—	—
11 hours	1.5	1.4–1.7	3
Time without exposure after 24 hours of exposure			
30 minutes	7.5	7.2–7.8	3
1 hour	6.7	6.4–7.1	3
2 hours	5.8	5.6–6.2	3

SOURCE: Stewart, et al. (56).

Another set of contaminants probably present in a tobacco smoke-polluted atmosphere are the oxides of nitrogen. These, specificially NO and NO_2, have been shown to be present in tobacco smoke although the type most likely to be present in the atmosphere is NO_2. No measurements have been reported of the amount of NO_2 in smoke-filled rooms. The importance of obtaining and evaluating this information is stressed by the results of Freeman and Haydon and

their colleagues (*17, 18, 19, 27, 28*) and of Blair, et al. (*5*) who observed bronchial and pulmonary parenchymal lesions in rodents continuously exposed to low levels of NO_2.

Other experimenters have measured carboxyhemoglobin (COHb) levels in nonsmokers exposed to cigarette smoke pollutants. Srch (*55*) observed that the COHb level in two nonsmokers rose from 2 to 5 percent (that of smokers from 5 to 10 percent) when seated in the cigarette-smoke contaminated car mentioned above (exposure to 90 p.p.m.). Harke (*24*) reported that when seven nonsmokers were exposed for approximately 90 minutes to a "smoked" room containing 30 p.p.m. of CO there was a rise in COHb from a mean of 0.9 percent to 2.0 percent. In 11 smokers subjected to the same conditions, COHb rose from a mean of 3.3 percent to 7.5 percent. With improved ventilation of the experimental room, the COHb level decreased significantly.

The CO exposures and COHb levels reported above closely approximate the results obtained following experimental chamber exposure of humans to various levels of CO. The uptake of CO by the person depends on, among other parameters: CO concentration, previous COHb level, the level of activity, and the person's state of health. Equilibrium between CO concentration in the lung and in the blood requires over 12 hours exposure. However, as may be noted in table 1, reproduced from Stewart, et al. (*56*) and derived from measures of COHb in young sedentary males who were not smoking, over half of the equilibrium COHb level is reached within three to four hours of the onset of exposure. The equilibrium value associated with 100 p.p.m. is approximately 14 to 15 percent COHb. Exposure to 100 p.p.m. in the nonsmoker can lead to 3.0 percent of COHb within 60 minutes and 6.0 percent in two hours (*16*). Of equal significance is that COHb has a half-life of at least three to four hours in the body. As shown in table 1, the COHb level fell only to 2.7 percent in the two hours following cessation of exposure to 50 p.p.m. from the end exposure level of 3.7 percent. This lengthy half-life extends the period of effect of exposure to CO and provides for a buildup of COHb concentration from fresh exposures.

THE EFFECTS OF LOW LEVELS OF CARBON MONOXIDE ON HUMAN HEALTH

The data on the effect of low levels of carbon monoxide on human psychological and physiological function have been summarized in two recent publications (*8, 58*).

There is presently much discussion as to the physiologic and psychophysiologic effects of exposure to levels of CO approximating 50 to 100 p.p.m. Beard and Grandstaff (*4*) observed that exposure to 50 p.p.m. of CO for from 27 to 90 minutes altered auditory dis-