nonsmokers, with a trend of increased risk with increased number of cigarettes smoked.

In Israel, the lifetime prevalence of PUD is 89/1000 men (*37*), similar to that in the United States. Smokers or ex-smokers had a prevalence of PUD (primarily duodenal) of 10.2 percent compared to 6.2 percent of nonsmokers (*25*). These differences were highly significant. Medalie, et al. made the interesting observation that as the smoking habits of first-generation Israelis of European descent increased, so did the prevalence of duodenal ulcer in this group (*37*).

Thus, when the question, "Do cigarette smokers have more peptic ulcers than nonsmokers?" is asked, results are strikingly consistent. Table 1 lists the six studies which investigated this problem (*22, 23, 25, 28, 31, 41*) with a summary of their characteristics and results. In each of the studies there was an increased prevalence of PUD in cigarette smokers compared to nonsmokers. Despite the fact that these studies were done at different times and in four different countries, the ratios for men are very similar, the median being 1.7 and the mean 1.9. The ratios for women are similar with the exception of the Polish study, in which very few women smoked. The ratios for ex-smokers (not shown) are also consistently greater than 1.0. In addition, the majority of the studies provided evidence of increased frequency of peptic ulcer with increases in the amount smoked.

Course of Peptic Ulcer Disease

Since cigarette smoking appears to be related to the prevalence of PUD, several other issues must be addressed. First, if a smoker does develop PUD, will cigarette smoking influence its healing and should the patient therefore be advised to stop smoking? Second, what, if any, role will smoking play in the chances of the patient dying from PUD?

Effect on Healing and Recurrence

In a classic study, Doll, et al. (*18*) examined the effect of continued smoking on the healing rate of gastric ulcers. Of the 80 smokers in the study, half were advised to stop smoking, the other half were allowed to continue smoking. Treatment for the ulcer disease was otherwise equivalent (although not the same for all patients). The investigators then compared the two groups in regard to percent showing marked healing of the ulcer at 4 weeks (marked healing is defined as 2/3 or greater reduction in ulcer size). Of those who were advised to discontinue smoking, 75 percent showed marked healing, compared to only 58 percent of those who continued to smoke. In fact, 45 percent of the patients advised to stop smoking did not do so completely. Of those who did, 86 percent (19/22) healed as opposed to 61 percent of those who only decreased their smoking. The healing rate of the 24 nonsmokers was 58 percent, similar to that of smokers. Study design

and technical aspects were offered as explanation for this latter observation.

Herrmann and Piper (*27*) retrospectively looked at 101 patients with benign gastric ulcer, all radiologically diagnosed. At 3 weeks, 67 percent of nonsmokers had healed compared to 43 percent of smokers who continued smoking. Differences were less marked at 6 weeks (85 percent vs. 75 percent). Although the numbers were smaller, those smokers who stopped did not do as well as either of the other two groups. The mean ulcer size in smokers was larger than in nonsmokers (120 mm^2 vs. 40 mm^2). Those who smoked cigarettes and ingested salicylates had the largest ulcers, but mean ulcer size was significantly larger in smokers than in nonsmokers, even when those ingesting salicylates were excluded.

Piper, et al. (*44*), while investigating gastric ulcer, noted increased rates of recurrence for those discharged unhealed, for those with larger ulcers, and for smokers. In a 4-year follow-up study of these patients, Piper, et al. (*46*) recently confirmed their previous report. They found that, of the 33 patients who were discharged with unhealed ulcers, 47 percent (8/17) of nonsmokers had recurrence, whereas 75 percent (12/16) of smokers had recurrence.

Only one study has been made on the effect of smoking on the healing of duodenal ulcers. Peterson, et al. (*42*) recently showed for the first time the efficacy of antacids over placebo in the healing of duodenal ulcer (Table 2). In this study, 78 percent of the antacid-treated group healed at 4 weeks as compared to 45 percent of the placebo group. When these groups were broken down into smokers and nonsmokers, 69 percent of the ulcers of nonsmokers who took placebo healed versus 32 percent of ulcers of smokers who took placebo ($p < .05$). In the antacid group, 87 percent of nonsmokers healed versus 75 percent of smokers ($p > .05$). Nonsmokers showed good healing even on placebo; antacids appeared to make the most difference in treating the duodenal ulcers of smokers.

Although there have been many recent clinical trials concerning the treatment of both gastric and duodenal ulcers using the new histamine H_2 receptor antagonist, cimetidine, none of these has carefully addressed the question of the influence of smoking on healing rates (*67*). Certainly, with all the international trials being undertaken to evaluate the plethora of new ulcer treatments, such as cimetidine, prostaglandins, bismuth, etc., the smoking habits of the patients should be examined. Such studies would provide information on the effect of smoking on the healing of untreated ulcers and on whether any of the treatments can overcome the presumed adverse effect of smoking on healing.

In summary, cigarette smoking in males probably retards the healing rates of both gastric and duodenal ulcers.

TABLE 2.—Percentage of patients whose duodenal ulcers were healed by endoscopic examination at 4 weeks, classified according to treatment with placebo or antacid and according to whether patients were smokers or nonsmokers of cigarettes. Numbers in parentheses are the number healed over the total number observed in each category.

	Percent healed at 4 weeks		
	Smokers	Nonsmokers	Total
Placebo	32% (8/25)	69% (9/13)	45% (17/38)
Antacid	75% (21/28)	88% (7/8)	78% (28/36)
Total	55% (29/53)	76% (16/21)	

SOURCE: Peterson, W. L. (*42*).

TABLE 3.—Ulcer mortality of male cigarette smokers and nonsmokers

Reference	No. of deaths	Rates: age-adjusted	Ulcer type	Mortality ratio	Dose response
Hammond, E.C. (1958)	62	yes	DU	2.2[a]	yes
(*26*)	46	yes	GU	>1.0[a,b]	yes
Dorn, H.F. (1959) (*20*)	51	yes	PU	2.8	yes
Weir, J.N. (1970) (*64*)	24	yes	DU	.5[c]	no
	20	yes	GU	>1.7[c,d]	yes
Doll, R. (1976) (*19*)	79	yes	PU	2.5	yes

[a]Smokers include regular cigarette smokers, many of whom also smoked cigars and pipes.
[b]Ratio is 46/0.
[c]Smokers include ex-smokers; nonsmokers include pipe and/or cigar.
[d]Ratio for smokers of 1 pack/day to those smoking less.
DU = deodenal ulcer; GU = gastric ulcer; PU = peptic ulcer.

Effect on Mortality

Mortality, as well as morbidity, in PUD is related to cigarette smoking. The four studies discussed below are summarized in Table 3. In one of the earliest and largest studies on smoking and death rates, Hammond and Horn (*26*) pointed out smoking's harmful influence on PUD. Deaths from duodenal ulcer for smokers of more than a half pack per day of cigarettes were 2.5 times the rate for nonsmokers; for those smoking one-half pack per day or less, the rate was 1.5 times the rate for nonsmokers. There were no gastric ulcer deaths among nonsmokers, but there were 46 among smokers; the death rate also increased with smoking more than a half pack per day of cigarettes. Thus, smoking was clearly associated with a higher occurrence of death in both types of ulcer disease.

Dorn (*20*), in another large study, had similar results. The ratio of observed deaths from both duodenal ulcer and gastric ulcer in smokers

to expected deaths from these diseases was 2.8. Those who smoked more than two packs per day had more deaths than those who smoked one to two packs per day, who in turn fared worse than those who smoked less than one pack per day.

In a prospective study of smoking and mortality in 68,153 middle-aged men, Weir and Dunn (*64*), just as Hammond and Horn (*26*), found no deaths from gastric ulcer in nonsmokers but a significant number of smokers dying from gastric ulcer disease. Their results, however, for duodenal ulcer were completely opposite, in that the relative risk of death from duodenal ulcer in smokers was half that in nonsmokers. Why this discrepancy should exist is not clear.

Doll and Peto (*19*), in a study of more than 10,000 British physicians, found a significant increase in death from peptic ulcer disease (specific location of ulcer not stated) in smokers as compared to nonsmokers, with a higher rate in moderate or heavy smokers than in light smokers.

Finally, Din and Small (*15*) proposed that the long-term survival of patients after gastrectomy was decreased by smoking. They felt the increased mortality rate was due to cigarette smoking (and perhaps alcohol, too) and not to the operation. The evidence for this is unclear.

A summary of the important data from the four studies (*19*, *20*, *26*, *64*) which bear on the epidemiological question, "Does smoking influence a person's chance of dying from his ulcer disease?" can be found in Table 3. These data show that mortality from gastric ulcer is greater in male cigarette smokers than in nonsmokers and, except in one study (*64*), also is greater in male cigarette smokers with duodenal ulcer disease. In the study that was the exception, the results are clouded by inclusion of ex-smokers in the smoking group. So, in general, it can be concluded that male cigarette smokers have more than a twofold greater chance of dying from ulcer disease than nonsmokers. It is not clear how much of this excess risk is due to the increased prevalence of ulcer disease in smokers and how much is due to the reduced ability of the smoker to survive an ulcer due to a greater prevalence of chronic heart and lung disease.

The Question of the Etiological Role of Smoking in Peptic Ulcer Disease

The studies reviewed have consistently shown an increased frequency of PUD in smokers as opposed to nonsmokers. In addition, the frequency of PUD rises with increases in the amount smoked, and smoking appears to retard peptic ulcer healing. All this, of course, does not provide a definitive answer to the question: "Is cigarette smoking a cause of peptic ulcer disease, or is it just associated with a cause such as genetic predisposition, personality type, and so on?" Epidemiological, case-control, and genetic studies cannot exclude the possibility that cigarette smoking is only associated with the cause(s) of PUD. An

essential link in establishing whether cigarette smoking is a causative factor in PUD is a convincing demonstration that smoking has an effect on physiological mechanisms that might allow an ulcer to develop. This question is difficult to deal with since it is still not known why certain patients develop PUD under any condition. We do know that (with rare exceptions) acid must be present (*30*). Although there is marked overlap with normals, on the average, patients with duodenal ulcer hypersecrete acid (*68*), so the effect of smoking on gastric acid secretion is of interest. Pancreatic buffering of acid may serve to protect the duodenum; does smoking interfere with this defense mechanism? Finally, since the pathogenesis of gastric ulcer may be different from duodenal ulcer (*49*), what other factors may smoking influence that might alter the stomach's defenses?

Gastric Secretion

Studies of the effects of smoking or nicotine on gastric acid secretion have been performed in rats, cats, dogs, and man—many with contradictory results even in the same species. One of the earliest studies (*53*) in dogs showed that neither cigarette smoking nor subcutaneous injections of 0.2, 0.4, or 1 mg of nicotine increased gastric acid secretion in the fasting state. Konturek, et al. (*36*) studied the effect of intravenous nicotine (100 μg/kg) in dogs and found no change in either basal acid output or half-maximal gastric acid secretion stimulated by histamine or pentagastrin. In addition, they found no effect on mucosal blood flow, and no interruption of the mucosal barrier to back diffusion of hydrogen ions by either intravenous or topical nicotine.

Nicotine, 100 μg/kg, injected into rats, depressed histamine-stimulated secretion of acid and pepsin. It also depressed basal secretion and submaximal pentagastrin-stimulated secretion. Tobacco smoke in 10 percent ethanol had no effect on acid secretion but reduced pepsin output (*56*). The effects of chronic nicotine administration in rats was also studied by the same investigators (*58*). Rats receiving 100 μg/kg nicotine 3 times daily for 15 days (the equivalent of smoking 10 to 15 cigarettes per day) doubled their gastric acid output and increased their pepsin output ($p < 0.01$). This effect could be blocked by either vagotomy or anterior hypothalamic lesions (*57*). Acute administration of nicotine to the chronically treated rats inhibited gastric acid and pepsin output. Robert and his colleagues have shown that nicotine can increase the number and severity of duodenal ulcers formed in rats by hydrochloric acid perfusion (*51*) or by subcutaneous infusion of pentagastrin and carbachol (*50*). Nicotine alone did not produce any ulcers in the animals.

Radecki, et al. (*47*) studied the response of cats to nicotine in both the basal and pentagastrin-stimulated states. Doses of nicotine up to 200 μg/kg did not alter acid secretion in either state. A dose of 400 μg/kg

depressed stimulated acid secretion by 30 percent; it also produced restlessness, vomiting, and diarrhea. Nicotine (200 μg/kg) did, however, potentiate the development of pentagastrin-induced experimental duodenal ulcers in these cats (*35*).

Studies of the effects of smoking on acid secretion in human subjects have given contradictory results. Schnedorf and Ivy (*53*) studied the effect of acute smoking on acid secretion in 40 normals (smokers and nonsmokers) and in 20 patients with duodenal ulcer. Mean acid output fell during smoking in both the normals and the ulcer patients, but no statistical analysis was done, so the significance of the decrease cannot be evaluated. Steigmann, et al. (*55*) reported that 26 of 44 controls and 40 of 45 ulcer patients increased acid production while smoking an unfiltered cigarette; a control study without smoking was not done. Cooper and Knight (*12*) recorded no difference in basal acid secretion between 60 patients with duodenal ulcer who smoked during the test and 60 patients who did not. Fung and Tye (*24*) investigated the effects of smoking 3 cigarettes per hour on 16 smokers and 16 nonsmokers, 23 of whom had duodenal ulcer and 7, gastric ulcer. There was no significant difference between basal acid output and acid output during smoking in either group. Another study showed that smoking four cigarettes an hour did not alter acid, pepsin, or mucus production in either normal subjects or ulcer patients who were smokers (*65*). This is particularly interesting in that the same laboratory reported different findings 15 years earlier when they found that smoking increased gastric secretion in man (*45*). Murthy, et al. (*40*) studied secretory response to smoking one cigarette per 15 minutes for 1 hour in smokers with duodenal ulcer and in normal smokers and nonsmokers. In the first 15 minutes, there was a significant increase in acid secretion in the ulcer patients. No significant effect was seen in either group of normals. Debas, et al. (*14*) studied 12 subjects, 6 smokers and 6 nonsmokers, of both sexes. The subjects smoked three cigarettes per hour while gastric secretion was maintained at half maximal rate with pentagastrin. Smoking caused no significant change in mean rate of acid secretion or pepsin secretion in either group. In a separate study (*10*), the same investigators found that while cigarettes alone had no effect on acid output, nausea induced by smoking in nonsmokers did inhibit acid production. Debas and Cohen (*13*) noted that smoking produced substantial inhibition of acid secretion in the majority of subjects during the first test but this could not be reproduced on repeated testing. They suspected that the inhibition was due to nausea, not smoking, per se. They also reported (*13*) that intravenous infusion of 2 mg of nicotine produced essentially no change in pentagastrin-stimulated acid and pepsin secretion in eight subjects.

Wilkinson and Johnston (*66*) also studied the effects of smoking on pentagastrin-stimulated acid secretion and found depression of acid output in response to smoking one or two cigarettes in three groups (38

percent in normals, 21 percent in duodenal ulcer patients, and 18 percent in gastric ulcer patients). All subjects experienced tachycardia and elevation of blood pressure while smoking.

In summary, most of the studies in human subjects have shown that smoking one or a few cigarettes exerts an inconsistent effect on acid secretion. A few studies found inhibition of acid secretion by smoking, but these involved first attempts at smoking with a gastric tube in place. Such procedures often produce nausea which by itself can inhibit acid secretion. There has been no systematic study of the effect of chronic smoking on acid secretion.

Pancreatic Secretion

It is generally accepted that an acid milieu is required for the development of duodenal ulcers; thus, smoking might influence duodenal ulcer formation by an effect on duodenal acidity. Smoking has not been clearly shown to increase gastric secretion, so perhaps it affects pancreatic buffering mechanisms. Murthy, et al. (*39*) showed that smoking may alter the duodenal environment. They found that smoking lowered duodenal pH from a range of 6.2–7.4 to 1.7–2.5 in five hypersecretors (BAO 5 to 16.5 mEq hr), but produced only a small effect in normal secretors.

Schnedorf and Ivy (*53*) found no significant change in either pancreatic or biliary secretion in dogs during smoking. Konturek and his colleagues (*36*) gave graded doses of nicotine (12.5 to 100 $\mu g\ kg^{-1}\ h^{-1}$ intravenously) to dogs on a background of maximal secretin stimulation and noted graded inhibition of bicarbonate secretion (23 to 62 percent). All values returned to control levels after cessation of the nicotine. Similarly, nicotine (100 $\mu g\ kg^{-1}\ h^{-1}$) reduced hepatic bile volume and bicarbonate by 50 percent. In a subsequent study (*34*), they reconfirmed that intravenous nicotine reduced the pancreatic response to intravenous secretin. Topical nicotine, however, did not alter the response to secretin. In addition, as the dose of secretin was increased from .37 to 3 U $kg^{-1}\ h^{-1}$, the inhibition of bicarbonate secretion by intravenous nicotine decreased from 75 to 15 percent. To examine the effect of nicotine on pancreatic secretion induced by endogenous secretin, pancreatic secretion was stimulated by intraduodenal administration of HCl with a response equivalent to .75 U $kg^{-1}\ h^{-1}$ of intravenous secretin. Both intravenous nicotine and topical nicotine reduced the response to the acid by about 25 percent. However, nicotine had no significant effect on cholecystokinin-induced stimulation of pancreatic secretion.

Boden and his associates (*7*) found in their dog experiments that basal and HCl (9.6 mEq/30 min) stimulated bicarbonate outputs were insignificantly decreased by intravenous infusion of nicotine (100 $\mu g\ kg^{-1}\ h^{-1}$), and nicotine did not decrease bicarbonate output in response to intravenous secretin (1.0 U $kg^{-1}\ h^{-1}$). In addition, nicotine had no

significant effect on the serum secretin level (measured by radioimmunoassay) except to delay the appearance of the peak value. It should be noted that Boden used 2.4 times as much acid to stimulate pancreatic secretion as did Konturek, et al. (*34*).

Solomon, et al. (*54*) studied the effect of nicotine on the rabbit pancreas. Nicotine infused at rates of 100 to 400 $\mu g\ kg^{-1}\ h^{-1}$ decreased pancreatic secretion in a dose-dependent fashion. Since nicotine is a stimulant of autonomic ganglia (*62*), the effect of norepinephrine and epinephrine was studied. Norepinephrine at 2 or 4 $\mu g\ kg^{-1}\ min^{-1}$ and epinephrine at 2 $\mu g\ kg^{-1}$ inhibited secretory flow and bicarbonate output. Phenoxybenzamine, an α-adrenergic blocker, increased water and bicarbonate secretion and blocked the inhibitory action of nicotine and norepinephrine on pancreatic secretion. On the basis of these results, they concluded that nicotine indirectly inhibits pancreatic secretion by stimulating catecholamine release, an effect that is negated by alpha adrenergic blockade.

The evidence for smoking's effect in man parallels that in animals. Bynum and his colleagues (*9*) studied the acute effects in light and heavy chronic smokers of smoking four cigarettes an hour on bicarbonate output in response to secretin. The light smokers responded normally to secretin during the control period but had decreased pancreatic bicarbonate output while smoking. Heavy smokers had a decreased response to secretin during the control period and this was not further affected by smoking. In a study of subjects who smoked regularly (*5*), smoking three cigarettes significantly decreased basal bicarbonate output.

Brown (*8*) investigated the effect of smoking on pancreatic secretion in 14 healthy smokers, 7 heavy and 7 light smokers. Heavy smokers had lower responses to secretin (2 U/kg) than light smokers. In addition, smoking cigarettes reduced even further the volume and bicarbonate content of the duodenal juice in both groups.

Murthy, et al. (*40*) studied the effects of smoking in smokers with and without duodenal ulcer and in nonsmokers. They found that smoking depressed basal bicarbonate and volume in both normals and patients with duodenal ulcer and in both smokers and nonsmokers. Changes in plasma nicotine were inversely correlated with pancreatic secretion. In addition, smoking had no effect on gastrin or secretin levels as measured by radioimmunoassay.

Bloom and Ward (*4*) reported depressed secretin release in response to intraduodenal acid instillation in patients with duodenal ulcer in contrast to controls. Actually, the increase in secretin over basal values was approximately the same in the ulcer patients as in the normal controls. Those patients who smoked more had smaller peak secretin values than lighter smokers. There was no difference in secretin release between smoking and nonsmoking controls. A subsequent study by Isenberg, et al. (*29*), using the same radioimmunoassay for

secretin, did not demonstrate a difference in secretin release between duodenal ulcer patients and normals. In light of this, the purported effect of smoking on secretin release must be questioned.

Four studies in man (*5*, *8*, *9*, *40*) all show decreases in bicarbonate output in response to smoking. There is no evidence that this is due to inhibition of secretin release.

Pyloric Reflux and Gastric Ulcer

What is smoking's relationship to the pathogenesis of gastric ulcer? The possible causes of gastric ulcer have been reviewed (*49*), and several hypotheses have been proposed. Various pharmacologic agents have been shown to disrupt the mucosal barrier to back diffusion of hydrogen ions, which might contribute to the development of gastric ulcer. However, no such effect has been demonstrated with smoking (*36*). Another hypothesis is that excessive reflux of duodenal contents, i.e. bile and pancreatic juice, through an incompetent pyloric sphincter, may be implicated in the pathogenesis of gastric ulcer (*52*). Recently, manometric studies of the human pylorus showed that smoking one cigarette decreased basal pressure significantly from 10.2 to 7.9 mm Hg (*61*). This supported previous work by Read and Grech (*48*) who found that smoking increased radiologic evidence of duodenogastric reflux. Whitecross, et al. (*65*), while studying the effect of smoking on gastric secretion, also noticed more marked bile staining of their gastric aspirates during the hour of smoking as compared to the control hour. Dippy and his colleagues found that smoking increased the degree of bile reflux in gastric ulcer patients (*16*).

Other possible etiological relationships have been examined. Edwards and Coghill (*21*) found that chronic atrophic gastritis was twice as common in persons who smoked more than 20 cigarettes a day as in nonsmokers. Since the majority of patients with gastric ulcer have chronic atrophic gastritis (*1*), smoking may predispose to gastric ulcer by producing chronic atrophic gastritis, which in turn may be a precursor of gastric ulcer.

Summary

If smoking does indeed influence the development and course of peptic ulcer disease, how does it do so? Experiments investigating the effect of smoking and nicotine on gastrointestinal function in animals and man have not established conclusively any mechanisms by which smoking might contribute to peptic ulcer formation. Most studies show little or no effect of smoking on acid secretion. Smoking and nicotine inhibit pancreatic secretion of bicarbonate; the consequent lowered capacity to neutralize gastric acid is a plausible but unproven mechanism by which smoking could favor occurrence of duodenal ulcer. Smoking also appears to increase reflux of duodenal contents into the stomach, which could be relevant in the light of the hypothesis

that injury to the gastric mucosa by bile acids and other constituents of duodenal contents is a factor in the pathogenesis of gastric ulcer.

Medical-Economic Implications

Peptic ulcer disease is one of the major health problems in the United States today. During their lifetime, about 10 percent of the persons in the United States can expect to suffer with this problem. Each year 400,000 patients are hospitalized and 150,000 undergo surgery for PUD. In addition, physicians see 2.5 million patients with peptic ulcers every year. Considering these facts, it comes as no surprise that, in 1975, the four million persons with ulcers cost the country an estimated $2.6 billion and are calculated to have cost it $3.7 billion in 1977 (*63*). These amounts include both medical care costs as well as indirect costs of earnings lost because of illness and disability and lifetime earnings lost because of early death.

Conclusions

The previous sections of this chapter have reviewed the various pieces of epidemiological and experimental evidence linking cigarette smoking with peptic ulcer disease. Three epidemiological questions have been addressed: (1) Does smoking increase the risk of getting an ulcer? (2) Does smoking retard healing of an ulcer? (3) Does smoking increase the risk of dying from ulcer?

Five studies show a higher proportion of smokers among PUD patients than among controls. Six studies show a greater prevalence of PUD among male cigarette smokers than among nonsmokers, the median ratio being 1.7. Results in women and the positive relationship between prevalence and amount smoked provide additional support. There is suggestive evidence for males that smoking retards ulcer healing. Four studies indicate that mortality due to ulcer is more than twice as high among male smokers as among nonsmokers.

What physiological effects produced by smoking might be relevant to the pathogenesis of ulcer? In regard to duodenal ulcer, evidence suggests that smoking inhibits pancreatic secretion of bicarbonate. As for gastric ulcer, smoking allows increased reflux of duodenal contents into the stomach. These effects, however, have not been shown to be directly related to the development of an ulcer.

Peptic Ulcer Disease: References

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10. ALLERGY AND IMMUNITY.

CONTENTS

Introduction

Tobacco and its products, including smoke, can affect the immune system in two ways. As antigens, they can interact with the immune system to induce specific responses evidenced by production of specific antibody or sensitized cells. Or, as irritant, pharmacologic, and toxic agents, they can interact with cellular elements of the host defense system, thereby influencing the functional ability of these elements.

Physicians have long noted the association between the development or aggravation of allergic or allergic-like symptoms and direct exposure to tobacco and tobacco products, including smoke, thus giving grounds for suspicion that tobacco can be causally related to the symptoms. There is evidence that tobacco smoke condensate can induce an immune response in animal models and in humans. The existence of a tobacco smoke allergy in humans is unproven, however, and is complicated by the difficulty of demonstrating a cause and effect relationship between the immunologic event and its manifestations.

The problem can best be understood by appreciating the current concept of that which characterizes an allergic individual—the ability to produce a unique serum antibody upon exposure to a given antigen. A property of that antibody is its selective fixation to cells located in certain tissues, such as skin and respiratory membranes.

Upon subsequent exposure, the antigen becomes bound at the cell surface by the preformed antibody. This phenomenon has been the basis of the skin test—an important aid in the diagnosis of allergy. In this procedure, introduction of the antigen into the skin, rendered sensitive by these previous events, induces pathophysiologic changes similar to those that occur in nasal and bronchial membranes upon natural exposure. The end result is an immediate wheal and flare inflammatory response.

Much of the past research in this area has relied heavily upon the use of skin tests. However, in the 15-year interval since the first Surgeon General's Report on smoking, research developments have made it possible to add new insights to the topic of tobacco allergy. In 1967, the Ishizakas (*51*) identified the skin sensitizing factor or reaginic antibody as immunoglobulin E (IgE), thus providing a major breakthrough in the understanding of allergy. Subsequently came descriptions of the specific localization of IgE on membranes of tissue mast cells (*111*) and the release of chemical mediators from the protoplasm of these cells when IgE reacts with corresponding surface antigens (*52*). In such instances, the antigen can be classified as an allergen.

Along with these advances came an appreciation of some of the limitations of skin testing. Among these is the fact that mast cell chemical mediators can also be released by nonspecific irritation (*81, 99*). Also, the presence of specific IgE fixed in the skin, as noted by the wheal and flare test response, is not the sole determinant for clinical expression of an allergy. Skin testing, done with appropriate materials

and controls, can give useful results to support a clinical impression, but it is not the sole diagnostic criterion.

Much of the previous work in assessing the possibility of tobacco allergy has been questioned because the extracts of the whole leaf or smoke used for skin testing represent a complex mixture of components; while one or more of the components may be allergenic, others are primarily irritant. However, a potential breakthrough has come about through the application of biochemical expertise in isolating and identifying a single component of tobacco which has been shown to cause positive, immediate reactions in skin tests in humans. (*9*, *10*). Whether this glycoprotein will ultimately be shown to be a causative agent of symptoms in humans awaits further study.

Even though skin testing remains the most sensitive indicator of reaginic antibody, in some cases there is reason to question its specificity. Verification of its validity is now possible because of the development of *in vitro* tests, such as the radioallergoabsorbent test (RAST) (*126*). While this assay is showing promise in diagnosis of pollen and insect venom allergy, further technology is required to make it suitable for general use. It may be possible to employ RAST in the study of tobacco smoke or leaf allergy, once the chemical properties of any true allergens that are discovered are characterized and adapted for the required solid phase studies.

The development of critical *in vitro* assays is important in the diagnosis of possible tobacco allergy because the nonspecific irritant qualities of tobacco extracts often leave the interpretation of skin tests and provocation tests in doubt. Awaiting such technology, several other approaches to exclude irritating effects have been employed: demonstration of the nonreactivity of the test extract in normal controls, end point titration, passive serum transfer (Prausnitz-Kuestner [P-K] test), and exhaustion of the response at the site of a passive serum transfer reaction by previous absorption of the test serum with a specific antigen.

Perhaps the term tobacco allergy has been used too loosely. In the past, reports of diagnosis have been based on a history of symptoms upon exposure to tobacco or its products, elimination of symptoms on withdrawal, demonstration of the occurrence of symptoms on reexposure, and emphasis on skin test results. These criteria must be reevaluated, since approaches for verification with precise methods and chemically-characterized specific tobacco antigen(s) are now on the horizon. In retrospect, it would appear that only those studies fulfilling a minimum set of criteria should have been considered acceptable as diagnostic of tobacco allergy. These criteria include the following:

1. Demonstration that tobacco smoke or a derivative product is capable of inducing those specific immune responses that are responsible for producing symptoms of allergy.

2. Demonstration upon exposure to tobacco smoke or a tobacco smoke product of reproducible symptoms characteristic of an allergic response, e.g., asthma, rhinitis or related upper respiratory symptoms, conjunctivitis, urticaria/angioedema, dermatitis, or anaphylactic shock. These symptoms must be reversible upon removal of tobacco or its derivatives; other possible effects of tobacco, such as irritant or pharmacological effects, must be excluded.

3. Demonstration of the affected person's ability to mount a reaginic response, as evidenced by an immediate wheal and flare response to the application of appropriate tobacco smoke extract by conventional prick, scratch, or intracutaneous routes, again provided nonspecific irritant properties have been excluded.

4. Demonstration of an association between the immunologically demonstrated reaction and the clinical symptoms. Further credence is given to this relationship if there is failure to manifest identical symptoms on exposure to potentially irritating gaseous or particulate matter that is not derived from tobacco.

While the discussion thus far and the thrust of this report will deal with the type of allergy known as immediate hypersensitivity, an additional fact to be considered is that tobacco can affect the immune system in a manner quite apart from the classic allergic state. It should be recognized that expressions of other immune mechanisms are often considered allergic. Thus, it is plausible that tobacco as an antigen could play a causative role in disease entities mediated by immunoglobulins in other classes (humoral IgG and IgM and secretory IgA at the mucous membrane surface). Direct cellular injury can arise from the action of cytotoxic antibodies, causing tissue inflammation by deposition of immune complexes through the sequence of antigen-antibody reactions, activation of the complement cascade, and migration of inflammatory cells into affected sites. In the case of delayed hypersensitivity, contact dermatitis of skin and mucous membranes emerges as a manifestation of cell-mediated immune mechanisms. Additionally, some physicians consider cardiovascular symptoms to be allergic because of the association of skin tests positive to tobacco extract with reproducible cardiac pathophysiologic expressions. However, exact differentiation between those responses that are truly immunologically mediated and those of pharmacologic idiosyncratic origin remains to be defined.

Though some of the reported studies may have adhered to one or more of the criteria listed above for diagnosis of an immediate allergic reaction, other demands of clinical investigation were not always met. Evaluation of many studies pertaining to tobacco allergy is difficult because of the lack of necessary data or because of poor experimental design. Controlled double-blind protocols have seldom been used. The presence of a positive skin test has been equated with the presence of clinical tobacco allergy, even in the absence of clinical

symptomatology. There have been failures in appreciating the role of tobacco smoke as a pollutant serving as a secondary or an aggravating factor rather than as an initiating agent, and provocative testing was not always carried out in patients in a basal asymptomatic state; thus, the influence of coincidentally present allergens and irritants could not be excluded. Other experimental deficiencies include failure to standardize the potency or antigenicity of extracts, inadequate definition of the term allergic when a subpopulation of "allergic patients" was studied, and failure to define the degree of exposure to tobacco among individual subjects.

When trying to compare studies, additional problems arise because of the many variables in the experimental protocols used. Criteria for scoring a skin test positive were not always defined, leaving no basis for comparison among different studies. Evident differences among the populations studied included age, sex, occupation, presence or absence of other allergies, environmental exposures, and smoking history. Additional variables included differences in source of tobacco used for testing, state of the tobacco (raw vs. cured), use of fractionated extracts as opposed to whole leaf extracts, differences in extraction methods, the presence or absence of additives or nicotine, and, most importantly, the use of smoke extracts as opposed to tobacco leaf extracts.

On the basis of clinical experience, many physicians are convinced that tobacco products can and do act through a primary allergic mechanism. However, this impression is not uniformly held and has not been unequivocally proven. That tobacco and/or its products can exacerbate underlying allergic conditions in both smokers and nonsmokers is generally accepted by clinicians on the basis of documented irritant and pharmacologic effects. Again, however, difficulties in the evaluation of studies examining these factors arise from problems in separating the effects of tobacco and smoke from other environmental allergens and pollutants and in knowing whether a given effect is primary or secondary.

The purpose of this chapter is to review critically the experimental evidence which may shed light on the unresolved relationship of tobacco smoking to allergy and other immune phenomena.

Basic Mechanisms

The term allergy, coined by Von Pirquet in 1906 (*115*), embraced any type of altered reaction to a substance brought about during the course of prior exposure. Hence, mechanisms both of enhanced resistance or immunity and of enhanced reactivity or hypersensitivity were referred to as the allergic state. During subsequent years, the term began to take on only the latter meaning; so that, currently, allergy is considered synonymous with hypersensitivity. Thus, whereas early in

the century allergy was given a broad scientific definition, the term is now more narrowly interpreted and, especially to a lay person, is associated with the symptoms of itching, sneezing, and wheezing characteristic of eczema, hives, hay fever, and asthma. Actually, however, there are several types of allergic states and their mechanisms are best understood in terms of the Gell and Coombs classification of hypersensitivity reactions (*23*).

1. Type I, or immediate hypersensitivity reaction, embraces the commonly-known classic allergic disorders mentioned above. A major portion of this report concerns itself with manifestations of this type of allergy; the details of its mediation involving the antibody known as IgE are presented in an earlier section.

2. Type II hypersensitivity is mediated by an antibody directed against a cell membrane or cell membrane-associated substance such as the injury to red blood cells that occurs during an incompatible blood transfusion. Serum complement is involved in this cytotoxic type reaction.

3. Type III is mediated by antigen-antibody combinations (immune complexes) resulting from their interaction and deposition in tissues. Serum sickness and the local Arthus-type reaction are the classic examples of this mechanism.

4. Type IV reaction is mediated by sensitized thymus-dependent lymphocytes (T cells), not by circulating antibodies. Contact dermatitis is an example of this delayed hypersensitivity reaction.

Tobacco as an Antigen

In order to demonstrate that any substance may be a cause of allergy, it is necessary (but not sufficient) to prove that the substance is antigenic. An antigen is capable of binding to the antibody whose formation it has induced, in humoral immunity, or is responsible for the development of sensitized cells, in delayed hypersensitivity. The term allergen has a slightly different connotation in that it is usually an environmental or food antigen to which only allergically predisposed individuals become specifically sensitized upon spontaneous contact by inhalation or ingestion. The mechanisms for allergenicity can proceed by any of the four types of hypersensitivity discussed above. There is evidence that tobacco leaf and its products are antigenic in animals and man, capable of both evoking a wide range of antibodies, including reaginic antibodies, and sensitizing small lymphocytes responsible for delayed type hypersensitivity (*4,41,53,60,80,104*). Evidence that tobacco smoke is antigenic in man, however, is meager and controversial at present.

There are several studies on experimental animals demonstrating stimulation of antibody production by tobacco products. Harkavy (*41*) injected rats with tobacco leaf extract. Upon subsequent challenge

with this material, he was able to demonstrate positive Schultz-Dale reactions with the sensitized intestinal strips. Armen and Cohen (*4*) were able to raise precipitating antibodies in rabbits injected with an extract of cured tobacco leaves but found this material to be weakly antigenic, requiring simultaneous injection of an adjuvant to induce the responses. Panayotopoulos, et al. (*80*) described the isolation of five components from tobacco leaf extracts capable of inducing precipitating antibodies. Recently, a mouse model for production of IgE and reaginic IgG against tobacco components has been developed by Justus and Adams (*53*), with identification of the antibodies by passive cutaneous anaphylaxis assay. Of potential importance are recent studies by Lehrer, et al. employing tobacco smoke and smoke in combination with host protein carriers. In these studies, sera from rabbits immunized with tobacco smoke components reacted by immunoprecipitation with tobacco smoke or leaf antigens (*62*). These investigators have also demonstrated reaginic antibodies in the sera of mice immunized with smoke extracts.

Human studies have also been revealing. Kreis, et al. (*60*) demonstrated that two of the five tobacco components inducing antibody formation in rabbits also reacted *in vitro* with human sera. Since these antigenic components were identified only in tobacco leaf extracts and not in the smoke, it was suspected that some contact with the leaf or cross reacting antigens must take place in humans. In the studies by Panayotopoulos, et al. (*80*), serum-precipitating antibodies to the five components of tobacco leaf were also identified in humans. Seventy-five percent of the subjects demonstrating this finding reacted with positive Arthus skin test reactions characteristic of this type of antibody when challenged intradermally with the extract, and smokers reacted more frequently than nonsmokers.

Of special interest and relevance are studies concerned with the demonstration of reaginic antibody against tobacco leaf in humans. This has been a controversial subject and is discussed in further detail in a later portion of this report. As early as 1923, Brown (*12*), attempting to demonstrate positive immediate skin tests to tobacco leaf extracts in humans, reported positive findings in 1 percent of asthmatic patients studied. This work was later extended (*9,10,38,42,43,64,83*) by workers who demonstrated not only the presence of positive skin test reactions to tobacco leaf extracts but also the ability to transfer this reaction passively to normal control subjects. Others (*20,104,105,113,124*), however,were unable to confirm the studies done with tobacco leaf extracts. Similar studies, perhaps more relevant to this report, have been done with extracts prepared from tobacco smoke, showing that these, too, are capable of reacting with reaginic antibody in humans (*9,10,85*). These studies were dependent primarily on skin reactivity, however, and, therefore, require further investigation. Delayed reactions following intradermal

test injections of tobacco extracts have also been reported in humans (*104*). This and other related studies discussed in a later section suggest that tobacco leaf may play a role as antigen in cell-mediated delayed hypersensitivity.

Identification of the Tobacco Antigen(s)

The tobacco plant is a member of the botanical family *Solonaceae*, as are potatoes and tomatoes. Since the raw leaf contains many high molecular weight proteins, theoretically it is potentially antigenic. In addition, the raw leaf may contain residues of insecticides or may be contaminated with bacteria, fungi, and even other known airborne allergens deposited on its surface, such as ragweed pollen. During curing and aging of the green leaves, chemical reactions take place within the tobacco leaf substance, and an array of additives further influences its composition. Aside from the exposure of tobacco and cigarette factory workers to raw and cured leaf, the possible antigens in tobacco smoke may be more relevant. Here again, this tobacco combustion product is a heterogeneous mixture of an estimated 2,000 particulate, gaseous, and semivolatile components (*75*). Furthermore, recent investigations show differences between the puff of smoke actively inhaled through the cigarette by the smoker and the so-called side-stream smoke discharged into the air by the burning cigarette tip, a source of potential inhalation by exposed nonsmokers (*48*). The issue is further complicated by the fact that tobacco and its products have both irritant and pharmacologic effects which can be mistakenly interpreted as allergenic. Isolation and purification of one or more substances responsible for the antigenicity of tobacco and its products will be necessary to clarify these findings.

Harkavy (*39, 40*) has shown that nicotine is not the responsible antigenic component of tobacco leaf, although its role as a hapten (*68*) is a possibility. Chu, et al. (*21*) have isolated five protein carbohydrate complexes with molecular weights varying between 20,000 and 60,000 from aqueous extracts of cigar and pipe tobacco. Kreis and coworkers (*60*) reported that two components of a soluble extract of tobacco leaf capable of stimulating antibody formation in rabbits and precipitating with human sera had molecular weights of 10,000 to 30,000. In another study (*80*), five antigenic plant proteins, immunoelectrophoretically localized in positions corresponding to the α_1-, α_2-, and β-globulins and isolated from the leaves of *Nicotiana tabacum*, had the property of precipitating with human sera. Differences in antigenic reactivity were described among different varieties of tobacco leaf tested. Because the serum precipitins were more prevalent in smokers, these investigators proposed that antigenic substances were carried in smoke passing through the cigarette, thus exposing the smoker. However, they did not attempt to demonstrate these substances in the tobacco

smoke. Becker, et al. (*9, 10*) reported that a tobacco glycoprotein gave positive and immediate skin test reactions in approximately one-third of the people tested, but the atopic status of these people and the irritant threshold of the extract were not determined.

Epidemiology

Few studies have attempted to relate the incidence of clinical allergy to active or passive effects of smoking. Asthma has occurred either in association with or following respiratory infections (*33*). Hence, any factor predisposing to infections of the lower respiratory tract, especially during childhood years, is relevant to this discussion on tobacco as a health hazard. One study (*75a*), surveying the incidence of respiratory symptoms and infections among 1,119 children, revealed that the percentage with symptoms increased with the definable level of smoking in the household. Another study, by Colley and coworkers (*22a*) surveying 2,205 infants, showed that the incidence of pneumonia and bronchitis in the first year of life was associated with parental smoking habits; the risk to the infant of parents both of whom smoked was almost twice that of nonsmoking parents. Cameron, et al. (*15*), in a survey of children from 727 families, found the prevalence of respiratory disorders to be 5.9 percent in homes where parents smoked compared with 3.1 percent in homes of nonsmoking parents.

Looking at the same problem from a different viewpoint, a study of hospital records of 10,762 infants by Harlap and Davies (*43a*) disclosed a significantly higher admission rate for bronchitis and pneumonia for those whose mothers smoked. It is, however, difficult to evaluate the impact of these infectious processes on the subsequent development of allergic diseases in the children studied because of several factors: differentiation among possible causative organisms (microbial or viral) was not always determined; the presence or absence of wheezing was not noted; and, apparently, follow-up studies were not undertaken.

Studies such as these also suffer from the criticism of failing to consider sufficiently other possible explanations for the increased prevalence of respiratory symptoms and disorders, such as socio-economic factors, genetic differences, and frequency of respiratory infection in parents. Thus, adverse consequences of passive smoking among healthy adults has been surveyed. Speer (*102*) examined the frequency of symptoms reported by 250 nonallergic, nonsmoking individuals, passively exposed in environments characterized by smoking. Nasal symptoms such as sneezing and itchiness were found in 29.2 percent, cough in 25.2 percent, headache in 33.0 percent, and eye irritation in 70.0 percent, emphasizing that irritant effects of smoke can simulate allergic symptoms.

As might be anticipated, persons with identified allergic disorders such as rhinitis or asthma have been more thoroughly investigated in

efforts to define causal connections between tobacco or smoke and their specific illnesses. Studies also have been made to ascertain whether smoking may aggravate preexisting allergic conditions. Zussman (*130, 131*) made an effort to learn whether tobacco leaf allergy played a causal role among allergic patients suffering from nasal, ocular, or bronchial involvement. Among a randomly selected group of 200 people, 16 percent were found to be clinically irritated by tobacco smoke. Thirteen of sixteen individuals manifesting positive skin tests to tobacco leaf extracts were reported to benefit from "desensitization" injections, in which tobacco extract was included among other allergens in the treatment mixtures. However, "benefit" was evaluated by the patient reporting without the advantage of objective assessment. It should also be noted that the tobacco leaf extract employed was contaminated with house dust antigen. In any case, the use of such a heterogenous mixture as tobacco extract in injection treatments is considered controversial.

In another study, Fontana and coworkers (*33*) found that 64 percent of 25 allergic children gave positive skin test reactions to tobacco leaf extract, compared with only 6 percent of nonallergic control subjects. Rosen (*91*) reported positive skin reactions to tobacco leaf extract in 12 percent of asthma patients, and Speer (*102*), in 15 percent of 191 allergically predisposed individuals. By retrospective survey, Pipes (*85*) made an effort to distinguish allergy to smoke from allergy to tobacco, noting that 13 percent of 370 allergic patients had positive skin test reactions to tobacco leaf extract. Ten percent of the study population also experienced aggravation of symptoms upon exposure to smoke, but none gave positive skin reactions to the tobacco smoke preparations utilized.

It is relevant to note that available tobacco leaf extracts utilized in skin testing are multicomponent mixtures that may contain both irritant and allergenic fractions and that it is a characteristic feature of the allergic state for an affected person to have positive skin reactions to allergenic extracts other than tobacco. Thus, the problem of precise interpretation of skin tests in clinical settings where allergic conditions have multifactorial features makes it impossible to determine what role, if any, allergy to tobacco smoke played in the clinical disorders of patients reported in these series. Fontana and coworkers (*33*) reported that 15 percent of 641 volunteers reacted with positive skin tests to one or more of the tobacco leaf extracts used, without a significant difference occurring between smokers and nonsmokers.

The above findings indicate that tobacco proteins are able to produce positive skin tests on an irritant basis. They further suggest that the predominant effect of smoke is an irritant superimposed upon an already pathophysiologically altered allergic membrane. In a study of 191 allergic nonsmokers and 250 nonallergic smokers, intolerance of tobacco smoke was a common occurrence in both groups (*102*).