guanosene 3',5-monophosphate (cyclic GMP) and may play a role in tissue proliferation and tumoregenesis, as well as exert effects on ciliary function and mucosal secretion in lung tissue.

Nitrogen Dioxide

Acute lung damage resulting from exposure to nitrogen dioxide at levels of 80 ppm for 3 hours has been reported by Langloss, et al. (*28*). Blank, et al. (*9*) exposed rats to levels of 15 to 40 ppm for up to 5 hours. Both of these groups reported alveolar damage with subsequent edema followed by hyperplasia or increased biosynthesis. The relevance of these types of exposure to smoking-related disease processes is unclear, however, since Norman and Keith (*34*) reported that nitrogen dioxide is present in cigarette smoke only in trace quantities.

Phenol

Little is known about the effects of phenol in smoke. Dalhamn (*14*), however, administered puffs of smoke from cigarettes with high and low phenol concentrations (18.8 and 2.7 mg/100 cigarettes versus a "normal" cigarette concentration of 7 mg/100 cigarettes) and found a clear correlation between ciliostasis and the phenol level in smoke. This area is one that should also be explored in more detail.

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Pharmacology of Cigarette Smoke

For the habitual smoker, the smoking of a cigarette is a rewarding experience, evidenced by the consumption of over 600 billion cigarettes annually in the United States. It is a reward which is highly anticipated by smokers, one that seems to satisfy a smoker's physiological and psychological needs.

Because of the myriad compounds present in cigarette smoke, it should be kept in mind that the pharmacological effects of smoking are not related solely to nicotine; rather, it is the combined effect of the whole smoke. Nevertheless, nicotine is generally accepted as the principal constituent responsible for cigarette smokers' pharmacologic response (*6, 20*), and will be reviewed on this criterion.

Nicotine is a powerful, quick-acting, ganglionic stimulant, eliciting its effects initially by depolarizing the ganglionic cells, stimulating both the sympathetic and parasympathetic ganglia (*15*).

Nicotine Absorption

Clearly, before any pharmacologic response can be elicited by nicotine from cigarette smoke, absorption must occur. The phenomenon of cigarette smoke absorption has been addressed by several investigators (*2, 4, 6, 9, 16*).

Some absorption takes place in the oral cavity. Based on monitoring carotid blood levels and radiolabeled nicotine cigarettes, estimates from three studies (*2, 4, 6*) show that less than 30 percent of the inhaled dose is absorbed. Further, Artho and Grob (*6*) observed that there were striking differences in nicotine absorption that are largely determined by the pH of the total smoke. The pK_b values of nicotine are 6.16 and 10.96 (*9*). From these data, the portions of the diprotonated nicotine and monoprotonated nicotine as well as the free nicotine can be calculated for a given pH. Because cigarette smoke typically has a pH of 5–7, the diprotonated form need not be considered in this discussion. The percentage of nicotine present as the free base is 0.40 at pH 5.35, 1.7 at pH 6, 15 at pH 7, 64 at pH 8, and 85 at pH 8.5.

The basic, lipid-soluble, uncharged nicotine is the form absorbed by the oral muscosa (*8*). A contributing factor to its absorption is that nicotine, as the free base, is volatile, which allows for rapid absorption from the gas phase. The relationship of the effects of pH are described in Figure 9 (*9*). Figure 10 (*4*) describes the oral absorption of nicotine from an identical dose of a buffered nicotine solution at pH 6, 7, and 8.

Nicotine which passes the oral cavity, as in cases of deep inhalation, is absorbed to a much greater extent than in the oral cavity. It is estimated that more than 90 percent of the inhaled nicotine is absorbed in the lungs (*2, 6, 16*). It should be noted also that retention of other cigarette smoke components by absorption is approximately 82 to 99

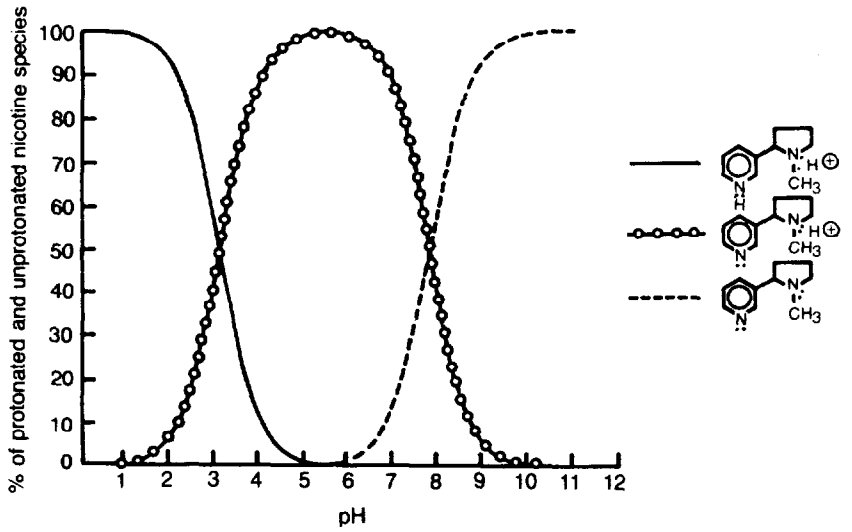


FIGURE 9.—Degree of protonation of nicotine in relation to pH (pH = pKa 10g 1 - α/α (Henderson/Hasselbach)).
SOURCE: Aviado, D.M., (7).

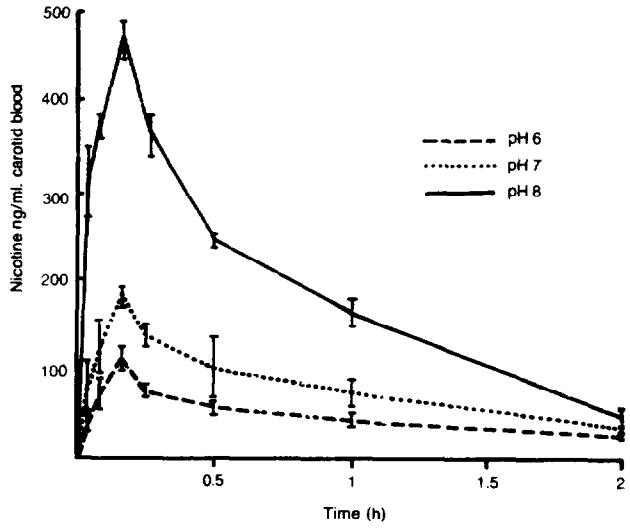


FIGURE 10.—Carotid blood levels of nicotine in ng/ml, after the presence in the mouth for 10 minutes of buffered solutions of nicotine at pH 6, pH 7, and pH 8. The bars show standard error of the mean.
SOURCE: Artho, A.A. (6).

percent, depending on the study. In any case, it is clear that the lung uptake of the nicotine in cigarette smoke is very efficient.

Whether cigarette smoke or a nicotine aerosol is used seems to make little difference on nicotine absorption in the lung. Herxheimer (*28*) found that inhalation from smoke and inhalation from a nicotine aerosol in approximately equivalent amounts (about 100 μg every 30 seconds) produced similar increases in pulse rate and blood pressure in healthy volunteers. The equivalence is only approximate, however, because the nicotine delivered per puff increases as the cigarette is smoked. This increase could explain why, although similar, the peak effects occurred later with cigarette smoking than with inhalation of the aerosol.

Although pH of the smoke is a major factor in nicotine absorption, other factors such as tobacco smoke contact time with mucus membranes, pH of the mucus membrane, pH of body fluids, depth and degree of inhalation, degree of habituation of the smoker, nicotine and moisture content, and puff frequency must be considered (*12, 20*).

Armitage, et al. (*3*) recently studied the effects of nicotine absorption in humans, comparing nicotine levels obtained in arterial blood. They found that arterial blood plasma concentrations of nicotine were comparable; however, the level rose more slowly in the smokers of small cigars. This may be due to a greater amount of the small cigar smoke being absorbed via the oral cavity as compared to cigarette smoke, which is primarily absorbed via the lung.

Alteration of Enzyme Systems

The nature of tolerance to nicotine and tobacco smoking has received attention and a complex picture has emerged (*25*). Studies with humans using high and low doses of nicotine presented apparently conflicting results regarding nicotine-cotinine metabolism. The authors suggested that acute high doses of nicotine produced inhibition of nicotine metabolism while lower daily doses on chronic exposure produced induction of the enzyme systems. These results are not uniformly accepted, however (*51*).

Gorrod and Jenner (*25*) concluded that the effect of nicotine is complex, but that the data suggest the importance of dosage, length of administration, and stress-induced effects. They also stated that a component of cigarette smoke other than nicotine may be responsible for the changes in nicotine metabolism observed in humans. In any case, tobacco smoke is a known inhibitor of enzyme systems, including dehydrogenases and oxygenases, so that inhibition of nicotine metabolism or other metabolic products is a distinct possibility (*27*).

Catecholamine Responses

Since nicotine is a ganglionic stimulant on both the sympathetic and parasympathetic nervous systems, it is not surprising that investiga-

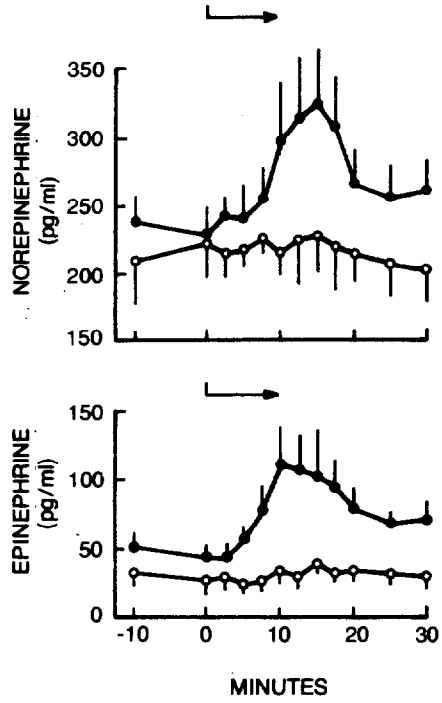


FIGURE 11.—Mean (± S.E.) plasma norepinephrine and epinephrine concentrations in association with smoking (closed symbols) and sham smoking (open symbols). The arrows indicate the period of smoking (or sham smoking).
SOURCE: Cutting, W.C. (*15*).

tors have looked at catecholamines as possible indicators of the nicotine-induced effects. Moreover, the catecholamines are usually considered to be released in stress-related responses. The source of the catecholamines is reported to be in the myocardial chromaffin tissue and the adrenal gland (*11, 29, 34*), and therefore consistent with this hypothesis.

Armitage (*1*) claims that the amount of nicotine inhaled during smoking is sufficient to cause release of catecholamines, but there is not uniform agreement on this subject (*60, 63*). Timing may be a critical factor in determining any catecholamine response because the response is likely to be transient. Cryer and coworkers (*14*) have graphically shown the rapid response of nonepinephrine and epinephrine as a consequence of cigarette smoking (see Figure 11).

Naquira and coworkers (*48*) studied the chronic administration (14 days) of nicotine in rats. They observed increased tyrosine hydroxylase

and dopamine-β-hydroxylase in the hypothalamus and adrenal medulla, but did not observe changes in tyrosine hydroxylase in the striatum. The data suggest that chronic nicotine administration can produce similar long-term alterations in both catecholamine-forming enzymes in the hypothalamus and adrenal medulla.

Catecholamines, released as a consequence of the nicotine-induced response, have been associated with or implicated in several biological responses. Cardiovascular-related diseases, bronchoconstriction and related pulmonary manifestations, fat metabolism, hyperglycemic effects, and the patellar reflex response have implicated catecholamines as being either directly or indirectly involved in these biological endpoints.

In the United States, more people die from coronary heart disease than from any other disease, and heart disease is the single most important cause of death among cigarette smokers(*62*). Epidemiological studies such as those reported by Mulcahy, et al. (*45*) who found a positive association between coronary heart disease mortality rate and the calculated per capita cigarette consumption in 21 countries, the Framingham study (*19, 23, 33, 50*), and reviews by Aronow (*5*) and Kannel (*32*) leave little doubt as to the consequences of cigarette smoking with respect to heart disease.

Cardiovascular and Related Effects

It is generally agreed that the acute cardiovascular effects of tobacco smoking can be attributed to the nicotine content of the cigarette and the amount absorbed (*14, 20*); similar effects have been observed by Irving and Yamamoto on administration of a comparable amount of nicotine by injection (*31*). The responses observed are those expected from stimulation of the sympathetic nervous system (*15*), including stimulation of the sympathetic ganglia, adrenal medulla, and the release of endogenous catecholamines (*14*). Responses are known to include increased heart rate and blood pressure (*2, 28*), cardiac output stroke volume, velocity of contraction, myocardial contractile force and oxygen consumption, and coronary blood flow and arrythmias (*15, 20*). Activation of the chemoreceptors of the carotid and aortic bodies results in vasoconstriction, tachycardia, and elevated blood pressure. Nadeau and James (*47*) have shown that the cardiac/stimulating effect of nicotine can be attributed to vagal stimulation. The possible role of elevated serum corticoids, following smoking of high nicotine cigarettes, in sensitizing the myocardium to the effects of the catecholamine has been suggested (*5, 29*) as also possibly contributing to ventricular arrythmias and myocardial infarctions. Further research has been suggested to resolve this issue (*5*).

Armitage and coworkers (*3*) have graphically described the dose-response effects of nicotine intravenous injection and cigarette

smoking as they affect blood pressure and heart rate. These results are described in Figure 12.

Pulmonary Effects

The respiratory effects of nicotine from smoke exposure are more difficult to quantify than cardiovascular effects because respiratory function may also be influenced by the solid particles or gases in cigarette smoke (i.e., CO and CO_2). For example, Reintjes and coworkers (*50*) were able to show that airway resistance values obtained immediately after smoking were elevated, but they did not identify the response as being caused by the nicotine in cigarette smoke. Aviado and coworkers (*7*) demonstrated that cigarette smoke causes acute bronchoconstriction by release of histamine and by stimulation of the parasympathetic nervous system in the lungs. Similar responses were shown to occur with arterial injections of nicotine. The effect is followed, however, by bronchodilation attributed to sympathetic stimulation.

Fat Metabolism

Changes in free fatty acids and mobilization of free fatty acids (FFA) have also been reviewed (*40*) as secondary effects of catecholamine stimulation. Kershbaum and coworkers (*35*) were led to the conclusion that nicotine had no direct lipolytic effect on cat or dog adipose fat tissue. Their findings lent support to the concept that mobilization of FFA by nicotine and cigarette smoke was a result of their stimulation of sympathetic nervous system activity and catecholamine secretion. In a related study (*36*) comparing 4 mg of nicotine in intravenously- and intratracheally-administered cigarette smoke, the authors suggested that tobacco smoking and nicotine caused an increased utilization of FFA in addition to their known effect of FFA mobilization. It was suggested that the greater FFA utilization was caused by increased cardiac output due to nicotine. The authors further suggested that nicotine changes the ratio of FFA incorporated into neutral lipid and phospholipids.

Hyperglycemic Effects

Another secondary response to the catecholamines present in the blood stream is believed to be a hyperglycemic condition as described in a recent review (*40*). Such a response would be consistent with a stress-related situation requiring an energy source for quick response. Milton (*44*) has suggested that in cats the hyperglycemic mobilizing action of smoking doses of nicotine is due entirely to stimulation of the adrenal gland, while the hyperglycemic effect at high doses is presumably due to stimulation of ganglia throughout the body resulting in the release of more epinephrine.

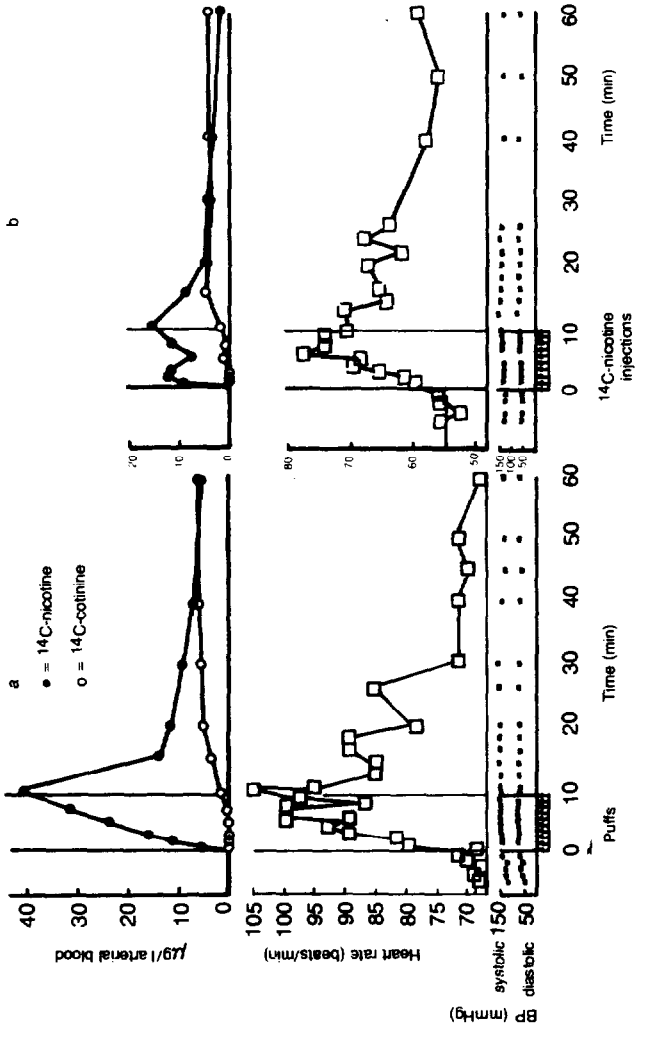


FIGURE 12.—Arterial blood levels of ^{14}C-nicotine (●) and ^{14}C-cotinine (○), heart rate (□), and blood pressure (■) during and after smoking a cigarette labeled with ^{14}C-nicotine (a), and during and after intravenous administration of 1 mg ^{14}C-nicotine in 10 divided doses (b).

SOURCE: Beckett, A.H. (*8*).

Other Central Nervous System Effects

It has recently been reported that nicotine also causes a diminution in the monosynaptic patellar reflex (*18*). This reduction in the patellar reflex was not seen after smoking nontobacco cigarettes. The effect thus appears to be closely related to nicotine. This was later confirmed by Domino and Baumgarten (*18*) after studying the response to an inhaled nicotine aerosol.

Metabolism of Nicotine

The metabolism of nicotine has been examined and reviewed by several investigators (*25, 27, 61*). The major part of the absorbed nicotine is metabolized rapidly in the body, and studies have established the liver as the major organ of detoxication. McKennis, et al. (*20a–20d*) have demonstrated that cotinine is the major metabolite of nicotine in human and animal urine. Other detected metabolites are summarized in Figure 13. Hansson and Schmiterlow (*27*), using radiolabeled nicotine, were able to detect radiolabeled products only in cotinine and CO_2. In studying tissue slices, they determined that nicotine is metabolized in the kidney and lung as well as in the liver, but not in the brain, diaphragm, spleen, stomach, small intestine, or adrenal glands.

Armitage (*2*), in comparing the effects of injected nicotine and innaled cigarette smoke, found that the half-life of nicotine in the arterial blood of smokers ranged from 24 to 84 minutes, with a mean value of 40 minutes when only the inhalation experiments were taken into account.

In examining the relationship between intravenous injections of nicotine and subsequent metabolism, Miller, et al. (*43*) found nicotine had a $t^1/_2$ of 55 to 64 minutes, with peak levels in the range of 297 ng/ml of plasma. While there was no effect of the administered dose on disappearance rate, there was a suggestion that the dose affected the distribution of nicotine. This would appear reasonable, in view of the known vasoconstrictive properties mentioned earlier, and could explain some of the conflicts in characterizing nicotine's pharmacologic properties.

Tsujimoto and coworkers (*59*) studied the tissue distribution of nicotine in dogs and rhesus monkeys. Five minutes after injection the adrenal medulla and cerebral cortex contained the highest concentration of nicotine. Other tissues containing significant quantities of nicotine included the spleen, adrenal cortex, kidney, and pancreas.

The effect of urinary pH on the excretion of nicotine and its metabolites has been studied by Beckett, et al. (*8*), Gorrod and Jenner (*25*), and Feyerabend and Russell (*21*). They determined that the amount of unchanged nicotine excreted in the urine after oral administration was dependent on pH, while cotinine was dependent on

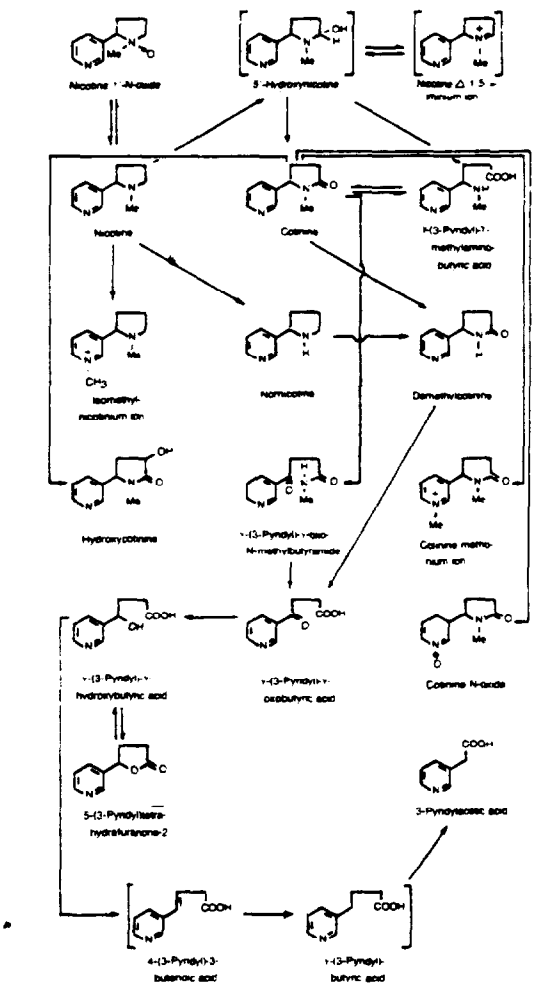


FIGURE 13.—Nicotine metabolism.
SOURCE: Hansson, E. (*27*).

urinary pH and flow rate. Specifically, the more acidic the urine, the larger the amount of unchanged nicotine. Similar results were obtained by Schachter and coworkers in reviewing the effect of urine pH as a result of stress-related factors (*55, 56*).

Metabolic Products in Test Animals from Nicotine in Cigarette Smoke

Investigations of nicotine metabolites from cigarette smoke, using various animal systems including man (*25, 27*), has led to the identification of several metabolites. An extensive investigation of

nicotine metabolites has been performed by Gorrod and Jenner (*25*). In the mouse, the metabolic products identified were cotinine, hydroxycotinine, γ-(3-pyridyl)-γ-oxo-N-methylbutyramide, CO_2 and two unidentified products separated by chromatography (*27*). The primary metabolites identified by Gorrod and Jenner include nicotine-1'-N-oxide, 5'-hydroxycotinine, cotinine, nornicotine, and isomethylnicotinium ion (*25*). Other metabolic products (Figure 13) are considered to be derived from those mentioned above. Only cotinine and nornicotine have been examined for their pharmacologic activity in any detail; these will be discussed below.

The complex mechanism by which cotinine, the major metabolite, is formed involves at least two enzyme systems. Both 5' hydroxynicotine and nicotine $\Delta N^{1'}(5')$ iminium ion have been implicated as intermediates (*30, 46*). Cotinine is further metabolized by pyrrolidone ring hydroxylation; all other metabolites of nicotine are thought to arise by cleavage of the phrrolidone ring of cotinine.

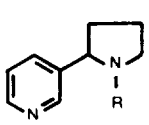
Related Alkaloids and Their Metabolites in Cigarette Smoke

It is difficult to generalize regarding the amount of various alkaloids other than nicotine in cigarettes because of differences in the alkaloid content and composition of the various tobacco strains employed in cigarette manufacture. However, nicotine is usually considered to account for about 95 percent of the alkaloids in tobacco. The remainder consists of varying proportions of nornicotine, anabasine, myosmine, anatabine, nicotyrine, and other alkaloids described in Figure 14 (*38*).

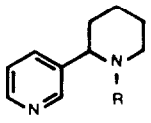
As stated above, nicotine is considered to be primarily responsible for eliciting the pharmacologic effects in cigarette smoke. Nevertheless, Using a battery of tests, Clark and coworkers (*13*) compared the pharmacological activity of a number of the minor alkaloids known or suspected to occur in tobacco smoke. Their results are summarized in Table 21. It should be noted, however, that only nicotine was optically pure. Others either were prepared synthetically, yielding racemic products, or were isolated under conditions resulting in optically inactive forms; therefore, the pharmacological responses reported may be less than would have been obtained had the optically active compounds (where appropriate) been tested. The LD_{50} values of several alkaloids in various species have been tabulated (*57*). Extrapolation of these data to other species and to the effects of multiple dosing, however, may not be useful because of variation in metabolic pathways among species.

Pharmacodynamics

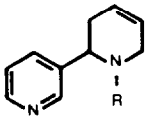
Until recently, relatively little attention was devoted to the pharmacodynamics of cigarette smoke. However, with increasing interest in smoking cessation techniques (*42*), tobacco industry emphasis on



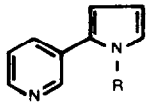
R = H, Nornicotine
R = CH_3, Nicotine



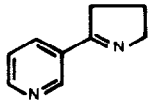
R = H, Anabasine
R = CH_3, N-Methyl-anabasine



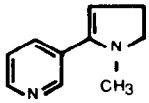
R = H, Anatabine
R = CH_3, N-Methyl-anatabine



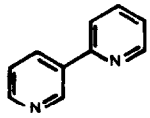
R = H, Nornicotyrine
R = CH_3, Nicotyrine



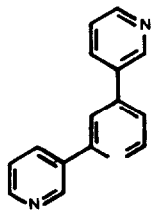
Myosmine



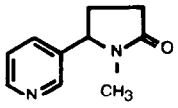
N-Methylmyosmine



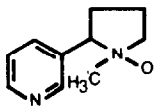
2,3-Dipyridyl



Nicotelline



Cotinine



Nicotine 1'-N-oxide

FIGURE 14.—Structural formulas of some tobacco alkaloids.
SOURCE: Larson, P.S. (*40*).

TABLE 21.—Relative molar potency of nicotine and other cigarette smoke alkaloids

Alkaloid	Contraction of guinea pig ileum	Pressor action in pithed rat	Release of catechol-amines from cat adrenal	Contraction of frog rectus	Blockade of contraction of diaphragm	Inhibition of cat knee jerk	Inhibition of cat flexor reflex	Inhibition of chick flexor reflex	Inhibition of chick crossed extensor reflex
Nicotine	100	100	100	100	100	100	100	100	100
Nornicotine	4.5	22	55	61	73	54	54	36	27
Metanicotine	4	3	20	–	<0.8	0.4	<0.6	–	12.5
Anabasine	17.5	20	75	28	50	17	33	33	20
Myosmine	0.2	5.5	–	3	12	3	<3	13	3
Nicotyrine	0.3	2.5	–	0.4	<0.08	17	<10	51	10
2:3-Dipyridyl	0.2	–	–	–	4	<0.1	<0.1	–	–
Dihydrometanicotine	<0.025	0.5	–	–	<0.8	<0.4	<0.6	–	–
N-Methylanabasine	<0.023	4.6	–	3	3.5	2	<5	–	12
Cotinine	<0.001	<0.1	0.03	–	<0.8	<0.05	<0.5	–	–
Nornicotyrine	<0.028	2	–	–	<0.9	–	–	–	–

SOURCE: Clark, M.S.G. (*15*).

lowering tar and nicotine in cigarette smoke (*49*), and major efforts undertaken in the research sector to develop and evaluate a less hazardous cigarette (*24*), the interactions between the physical/chemical characteristics of the cigarette and the behavioral/physiological characteristics of the smoker are being given increasing attention.

As discussed elsewhere in this report, there are many theories about why people smoke. While in most cases the explanation is not simple, nicotine is a generally agreed-upon factor. Nicotine has long been considered as habitual at least and, by some persons, as an addictive drug (*22, 37, 54*). The Third Report of the Royal College of Physicians of London (1977) is quite explicit in stating that "Tobacco smoking is a form of drug dependence different from but no less strong than that in other drugs of addiction" (*50a*). The pharmacodynamic implications of smoking have generated detoxification techniques in smoking-cessation programs, the search for nicotine substitutes or antinicotine drugs (e.g., lobeline (*26*)), the presentation of nicotine in an alternate vehicle (e.g., chewing gum (*52*)), and the evaluation of nicotine aerosol techniques in terms of their impact on modifying smoking behavior (*28*).

Because of the role of nicotine in creating a dependency for the smoker, it is appropriate to consider smoking patterns and the effects these patterns have on response to cigarette smoke components. There are many ways to characterize smoking patterns:

Type of cigarette smoked. Cigarette brands vary radically today in terms of nicotine and tar delivery and somewhat less in terms of CO, acrolein, HCN and NOx's.

Number of cigarettes smoked. This ranges from none to a maximum of about 100 cigarettes a day.

Amount of cigarette smoked. Smoking patterns range from smoking only the first few millimeters to smoking down to a few millimeters from the butt end. Inasmuch as the tobacco at the butt end of the cigarette acts as a filter and builds up nicotine and tar as the cigarette is smoked, the last few puffs on a cigarette smoked all the way down will have a much higher nicotine and tar delivery than the first puffs.

Number of puffs. This can range from one or two puffs up to about 20.

Depth of inhalation. Again, this can vary from the pattern of the noninhaler to deep inhalation.

Length of inhalation. The longer the cigarette smoke is held in the lungs, the greater the absorption and thus, the deposition of smoke.

Since it would be possible for an individual smoking 10 cigarettes per day to absorb more of the components of cigarette smoke than one who smoked many times that number, realistic evaluation of smoking impact calls for the development of dosimetric techniques applicable to research, screening, and smoking-pattern modification programs.

As might be expected, the smoking pattern affects absorption of the content of cigarette smoke, and consequently the toxic effects, differentially. Some of the contents and characteristics of the smoke also modify smoking patterns.

Since nicotine is absorbed through the mucus membranes and the skin as well as the alveoli, it will be absorbed, to a lesser degree, even by the noninhaler. (The nicotine from snuff and chewing tobacco is absorbed only through the mucus membrane route as is the case for most noninhaling cigar smokers.) Although the absorption of nicotine is to some degree independent of smoking patterns, there is significant evidence, not uniformly accepted, that a number of dimensions of smoking patterns are to a large degree dependent on nicotine content of the cigarette. Increasing evidence indicates that chronic "nicotine-dependent" smokers tend to titrate or compensate their inhalation profile in order to develop a desirable blood level of nicotine (*41*). This is done by modifying the number of cigarettes smoked, the number of puffs, the amount of cigarette smoked, or the depth of inhalation (*9*, *39*). The implication of this apparent compensatory modification of smoking pattern to assure a preestablished nicotine titration level in the smoker has broad ramifications when considered in the context of the increasingly popular lower-nicotine cigarettes designed to give low delivery. Since this is an area to which major attention has been devoted only recently, a serious research effort should be mounted in order to better understand this "titration" phenomenon. The implications for differential tax sanctions based upon nicotine delivery, as well as for the direction of development of less hazardous cigarettes, need exploration in depth. Since the pH of the urine affects the rate of elimination of nicotine from the blood stream, it might be expected to have an impact on the nicotine titration process with accompanying modification of smoking patterns (*53*); hence it should also be examined in greater detail.

Another characteristic of cigarette smoke which modifies smoking patterns is the pH (*9*). As has been mentioned earlier, cigarette smoke of the bright type or U.S. blending formula is mildly acidic, which results in relatively little irritation to the mucosa as compared to mildly basic smoke, and can accordingly be inhaled without unpleasant effects by many smokers. Cigar smoke, on the other hand, is mildly basic and is quite irritating to the mucosal tissues; for this reason, cigar smokers are less apt to inhale, or to inhale deeply, than are cigarette smokers. It has also been suggested that cigars are satisfying without being inhaled.

The remaining major toxic elements of cigarette smoke (CO and NO_x's) are absorbed primarily through the alveoli (acrolein and HCN are water soluble gases and are readily absorbed in the upper respiratory tract), and accordingly the inhalation characteristics of the smoker will have a direct impact on the short- and long-range effects

of these substances. Further, the ciliatoxic effects of HCN and the ciliastatic effects of acrolein will depend to a major extent on the inhalation pattern of the smoker. Lastly, the contribution of the NO_x's to chronic obstructive pulmonary disease depends to a major extent on the presentation of these substances at the alveolar site; as a result, inhalation practices will strongly affect the pathological sequelae of the NO_x compounds.

Thus, the consequences of cigarette smoking would appear to be dependent not only on the composition of the smoke itself, but also on the smoking patterns of the individual smoker. More extensive effort is needed to develop dosimetric and puff-analysis tools and techniques as a basis for better understanding of the pharmacokinetic and smoking behavioral dimensions of cigarette smoking.

Summary

The smoking of a cigarette seems to satisfy a smoker's physiological and psychological needs, and it is generally accepted that nicotine is the principal constituent responsible for cigarette smokers' pharmacologic responses.

Nicotine is rapidly absorbed in both the oral cavity and lungs, especially at basic pH. It is a quick-acting ganglionic stimulant on both the sympathetic and parasympathetic ganglia.

Nicotine causes the release of catecholamines, epinephrine, and norepinephrine. Several physiological responses have been attributed to nicotine and/or catecholamines, such as increased heart rate and blood pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, oxygen consumption, coronary blood flow and arrythmias, bronchoconstriction and related pulmonary manifestations, increased mobilization and utilization of free fatty acids, hyperglycemic effects, and a decreased pateller reflex response.

Considering the nicotine metabolites in cigarette smoke and the presence of minor amounts of related alkaloids, nicotine exerts the strongest response in a variety of biochemical and physiological tests.

Considerable evidence exists, although it is not uniformly accepted, that smoking patterns of chronic smokers are dependent on the nicotine content of the cigarette and dependent on what the nicotine delivery would be when measured by the standard methodology. Smoking patterns are dependent, to varying degrees, on the type of cigarette smoked, the number of cigarettes smoked, the length of the cigarette rod burned, the number of puffs, the depth of inhalation, and the length of inhalation. Nicotine absorption is also dependent on the above-mentioned parameters as well as on urine pH, which affects the rate of elimination of unmetabolized nicotine.

Pharmacology of Cigarette Smoke: References

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Reductions of the Toxic Activity of Cigarette Smoke

Gas Phase

During the last decade there has been a reduction in the concentration of toxic and tumorigenic agents in cigarette smoke. Measured on experimental animals, these reductions of harmful smoke constituents are reflected in diminished ciliatoxicity, overall toxicity, and tumorigenicity of low-tar, low-nicotine cigarettes.

Carbon Monoxide

Carbon monoxide is one of the compounds in cigarette smoke judged most likely to contribute to the health hazards of smoking. Certain modifications in the makeup and fillers of cigarettes, as well as the use of special preparations of charcoal in filter tips, can lead to a slight reduction of carbon monoxide in cigarette smoke (*32*); however, selective filtration of CO does not seem to be feasible. For certain filter cigarettes (those without perforated filter tips) the CO yield has remained comparable to that of nonfilter cigarettes or has even increased slightly (*40*). The major, and possibly the only, significant reduction of CO in cigarette smoke can be achieved by air dilution with perforated filter tips and/or perforated cigarette paper (*33*). With increasing air dilution, CO is selectively reduced as compared to tar and CO_2 (*27, 29*). This CO reduction occurs because the air dilution holes permit rapid diffusion out of the smoke stream and because lowering the effective puff volume through the fire cone alters the combustion process and lowers the CO:CO_2 ratio. As Table 22 shows, the CO reduction is greater with ventilation than the decrease in tobacco burned during puffing, as indicated by percent ventilation. For example, where the ventilation of a cigarette is 52 percent, the CO reduction is 67 percent. However, the smoker of cigarettes with perforated wrappers and/or ventilated filter tips may compensate for air dilution by taking increased puff volumes when he inhales. Overall, though, ventilated filters do improve the CO/nicotine ratio. At present, data on the carboxyhemoglobin levels of long-term smokers of these types of cigarettes are not available for comparison.

As expected, the smoke of cigars and pipes is high in CO because of the nearly complete lack of ventilation through the cigar wrapper or pipe bowl (*21, 30*).

Reduction of Ciliatoxic Smoke Compounds

It is assumed that mucociliary clearance is essential for the maintenance of a normal pulmonary environment. Any interference with the lung clearance mechanism can result in an accumulation of toxic and tumorigenic agents and, consequently, in respiratory diseases. Studies of humans have shown that in certain smokers, lung clearance returns to normal after 3 months' cessation of smoking (*5*). These consider-

TABLE 22.—Effects of various forms of air dilution on carbon monoxide and carbon dioxide deliveries

Sample	Ventilation	CO(mg)	CO_2(mg)
Filter Cigarette A perforated tip	22%	10.6	35.1
Filter Cigarette A unperforated tip		13.6	43.5
% reduction		21	19
Cigarette B with tip open perforated	43%	8.7	30.7
Cigarette B unperforated tip		17.2	52.3
% reduction		49.4	41.2
Cigarette C with line perforated paper	52%	5.6	30.4
Cigarette C without line perforations		17.1	57.4
% reduction		67	48.7

SOURCE: Sloan, C.H. (*31*).

ations have led to efforts towards the identification and reduction of ciliatoxic components in cigarette smoke. Bioassays for the evaluation of the ciliatoxicity of cigarette smoke and of individual smoke components are carried out with isolated ciliated tissues, with organs, or with the intact animal (*1, 43*).

While the particulate matter of cigarette smoke inhibits mucociliary clearance to some extent, certain volatile smoke constituents show significant ciliatoxic potency. Table 23 lists gas phase components with relatively high ciliatoxicity as measured on isolated chicken trachea (*1*).

One or more successful methods for the specific reduction of ciliatoxic volatiles in cigarette smoke is charcoal filtration, a technique thoroughly explored over many years (*13, 18, 44*). The efficiency for removal of gas phase constituents of charcoal filter tips is listed in Table 24 (*12, 31*). An extensive study demonstrated that air dilution filters lowered delivery of gaseous aldehydes, CO, HCN, etc. (*12*).

The design of cigarettes can also significantly influence the ciliatoxicity of the mainstream smoke. This is important since modification of the design characteristics of cigarettes is primarily aimed at lowering tar and nicotine content of smoke and may not concurrently consider ciliatoxicity of the smoke. Studies on the mainstream smoke of cigarettes made from certain reconstituted tobacco sheets or tobacco substitutes and on mainstream smoke of filter cigarettes with air dilution have shown a reduction in ciliatoxici-

TABLE 23.—Vapor phase constituents with high ciliatoxic potency—in vitro

Compound	Potency	Amount in smoke (μg/puff) Typical (Range)
Hydrogen Cyanide	+ + +	38(16–63)
Formaldehyde	+ + +	5(25–11)
Acrolein	+ + +	10(5.6–10.4)
Sulfur Dioxide	+ + +	<1
Crotonaldehyde	+ +	1.6
2,3-Butanedione	+ +	12
Ammonia	+ +	1
Nitrogen Dioxide	+ +	<10
Methacrolein	+	1
Vinyl Acetate	+	0.5
Nitric Oxide	+	60(12–75)

Score — ED_{50}(8 puffs) (μg/puff)
+ + + High = <50
+ + Moderate = 50–100
+ Low = 100–500
SOURCE: Battista, S.P. (*1*).

ty as well as lower levels of hydrogen cyanide, formaldehyde, and tar (*24–26*).

Volatile Phenols and Catechols

In the experimental setting, volatile phenols were considered to contribute to the tumor-promoting activity of cigarette smoke. Several studies have demonstrated that various types of cellulose acetate filter tips selectively removed volatile phenols from cigarette mainstream smoke (*10, 31, 44*). However, in bioassays on mouse skin with cigarette tar and in inhalation studies with diluted whole smoke on Syrian golden hamsters, a selective reduction of volatile phenols was not paralleled by a selective reduction of tumorigenicity (*8, 24–26*).

Catechols, which are known co-carcinogens in the experimental setting, are not selectively reduced by filtration from cigarette smoke (*3, 22*). Cigarette fillers low in wax layer components, either by use of tobacco stems, reconstituted tobacco sheet, or tobacco extracted with a hexane-ethanol mixture, delivered smoke significantly reduced in catechols (*6*). Although it has not been directly established that a selective reduction in catechol leads to a significant reduction of the tumorigenic potential of cigarette smoke, it is of interest that all those tars or whole smokes of cigarettes which are low in catechol also have a significantly lower tumorigenic activity (*7, 8, 24–26*).