TABLE 24.—Removal of some gas-phase components of cigarette smoke by an activated carbon filter*

Compound	Removal %
Methane	0
Acetylene	0
Ethane	0
Propene	26.2
Chloromethane	25.9
Propane	17
Methanol	51.9
Acetaldehyde	55.4
Butene	59.5
Ethanol	58.7
Acetonitrile	68.3
Acrolein	91
Acetone	78.9
Acrylonitrile	44.4
Isoprene	76.9
Pentadiene	96.5
2-Butanone	97.8
Hexane	73.9
Benzene	55
Dimethylfuran	95.4
Pyridine	92.5
Toluene	60

* 100 Mg activated carbon; Sample No. M-S-4.
SOURCE: Kensler, C.J. (*18*).

Volatile N-Nitrosamines

As discussed earlier, N-nitrosamine formation in tobacco smoke is determined by the nitrate content of the tobacco. Lowering of the nitrate content leads to a reduction of volatile nitrosamines, as has been demonstrated for the smoke of Burley tobaccos grown at varying rates of N-fertilization (*15*). Certain other agricultural practices can also lead to a reduction of volatile nitrosamines in the smoke of tobaccos (*38*). More importantly, however, selective removal (70 to 80 percent) of volatile nitrosamines from the smoke can be achieved by cellulose filters (*4, 38*). At present, it has not been demonstrated that a significant reduction of volatile N-nitrosamines will lead to a significant reduction of the tumorigenic potential of cigarette smoke. The detection of differences in the tumorigenic potential of the smoke of cigarettes which vary greatly in N-nitrosamine content (*23*) is likely to be difficult because of the low sensitivity of the experimental models presently available.

Particulate Phase

Tar

In the experimental setting, a dose response has been established between tar application or smoke inhaled and tumor yield (*2, 8*). These data support epidemiological findings relating the amount of cigarette smoke inhaled and the likelihood of cancer of the oral cavity, cancer of the lung, cardiovascular disease, and respiratory disease in humans (*14, 41, 45*). Thus, as long as warnings of health hazards from smoking are disregarded and as long as cigarettes are consumed, efforts towards a reduction of tar and smoke components which may contribute to these health hazards should be continued.

Several approaches affect tar reduction in the smoke by modification of the cigarette filler (*11, 44*), and many of these have, in fact, been applied to cigarettes manufactured in the United States and other countries (Figure 15). The most widely used techniques are summarized in Table 25. The application of a combination of these techniques has led to low tar cigarettes; air dilution of smoke is a prominent feature of many of the recently introduced low-tar brands (<10 mg). Homogenized leaf curing (*37*) and reduction of tobacco proteins (*34*) are currently being thoroughly investigated as additional methods for reduction of tar, nicotine, and other harmful smoke components.

Nicotine

Nicotine and the minor tobacco alkaloids are largely responsible for tobacco habituation, smoke flavor, and smoke toxicity and are the precursors for the tobacco specific N-nitrosamines. Since 1926, research programs have been directed toward the reduction of the tobacco alkaloids (*19*); a combination of methods has, in fact, led to a drastic lowering of nicotine in the smoke of U.S. cigarettes (Figure 16). The methods summarized in Table 25 for the reduction of tar in cigarette smoke apply also to the reduction of nicotine in the smoke. Selective reduction of tobacco alkaloids has been achieved by breeding specific varieties and by close spacing of tobacco plants. After harvesting the tobacco, leaf nicotine can also be selectively reduced by oxidation with bacterial enzymes, special curing conditions, reaction with alkylating agents, extraction with water and ammonia, and by steam distillation. Since cigarettes in the United States and in most foreign countries are made of flue-cured tobacco, are blends with flue-cured tobacco as a major ingredient or, in a few cases, are blends with Turkish tobacco, the pH of the resulting mainstream smoke is below 6.5 and thus essentially contains only protonated nicotine. Nicotine salts, however, are a part of the particulate matter and are, therefore, not amenable to significant selective filtration.

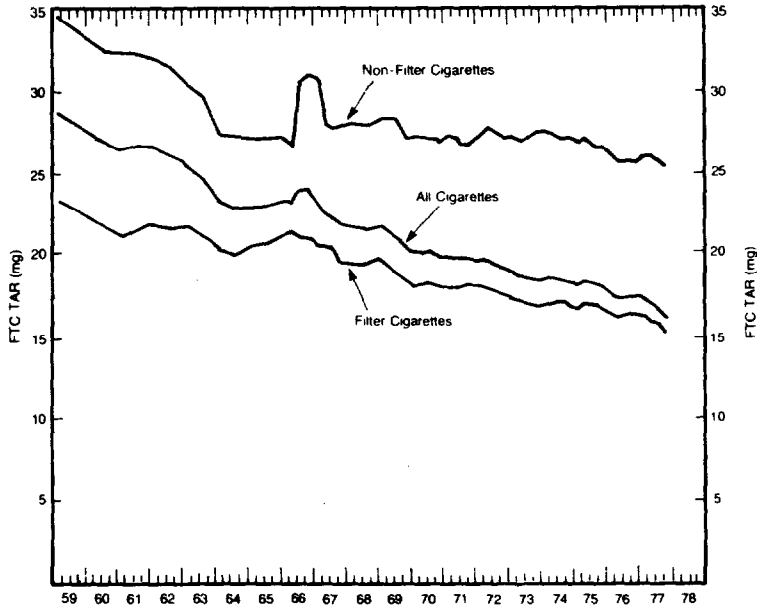

FIGURE 15.—Sales-weighted average "tar" deliveries of U.S. cigarettes from 1957 to the the present.

SOURCE: Wakeham, H. (*59*).

Polynuclear Aromatic Hydrocarbons

As early as 1957, it was demonstrated that polynuclear aromatic hydrocarbons (PAH) play an important role in tobacco carcinogenesis (*46*). When the PAH-containing neutral subfraction is removed from the tar, the carcinogenic activity of the PAH-free tar on mouse skin is reduced by more than 50 percent (*9, 17*). Detailed studies have shown that the PAH are the major tumor initiators in the smoke; a significant reduction of the polycyclic hydrocarbons leads to a concomitant reduction of the tumorigenic activity of the tar on mouse skin and of the whole smoke on the larynx of Syrian golden hamsters (*7, 12, 16, 20, 24, 25, 44*).

As discussed earlier, PAH are primarily pyrosynthesized from C,H-radicals. Therefore, their formation in smoke can be inhibited by radical scavengers. Thus, when nitrate levels in tobacco are increased, the nitrogen oxides formed in the burning cone serve as C,H-radical scavengers and inhibit PAH-formation (*28*). Since the mechanism of the pyrosynthesis of PAH from C,H-radicals is valid for most of the PAH in tobacco smoke, benzo(*a*)pyrene is often used generally as an indicator of PAH levels and specifically as an indicator of the carcinogenic potential of the smoke as measured in animal experiments. However, this "indicator" concept can be applied only to smoke

TABLE 25.—Some measures for "tar" reduction in cigarette smoke

1. *Agricultural Techniques*
   a. Genetics and breeding
   b. Planting density (plants/acre)
   c. Nitrate fertilization
   d. Application of agricultural chemicals
   e. Stage of topping
2. *Selection of Raw Tobacco*
   a. Tobacco type
   b. Stalk position
   c. Nitrate content
   d. Selection by specific tobacco constituent (e.g. protein, carbohydrates, resins)
3. *Treatment of Tobacco*
   a. Curling
   b. Homogenized leaf curing
   c. Grading
   d. Fermentation
   e. Extraction
   f. Tobacco expansion (freeze-drying)
4. *Tobacco Additives*
5. *Blending*
6. *Amount of:*
   a. Tobacco
   b. Stems
   c. Reconstituted tobacco
   d. Expanded tobacco
7. *Tobacco Cut*
8. *Smoke Dilution*
   a. Porous cigarette paper
   b. Perforated cigarette paper
   c. Perforated filter tips
9. *Smoke Filtration*

SOURCE: Tso, T.C. (*35*).

deriving from cigarettes primarily made up of the same precursor material, i.e., tobacco leaves. The "indicator" concept was applied in measuring BαP formation in many attempts to achieve PAH reduction in smoke. The PAH yield in smoke can be reduced selectively by

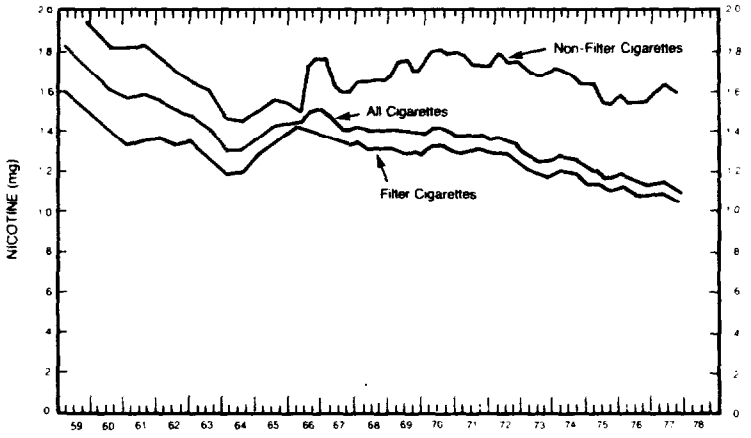

FIGURE 16.—Sales-weighted average nicotine deliveries of U.S. cigarettes from 1957 to present.

SOURCE: Wakeham, H. (*59*).

increasing combustibility of the cigarette filler, by reducing the wax content of the tobacco lamina, and by adding compounds to tobacco which provide radical-scavengers during burning of the cigarette, thus utilizing the concept of inhibiting PAH-pyrosynthesis as discussed above. Since PAH have low volatility, they are a part of the condensed smoke matter (tar) and cannot be selectively removed by filtration.

Increased combustilibity can be achieved by air dilution, by increasing the filling power of the tobacco blend, and by selection of tobaccos rich in nitrates or low in wax content. Combustion is also improved by addition of reconstituted tobacco sheet (RTS), expanded (freeze-dried) tobaccos, and tobacco substitutes with special physical characteristics. The reduction of the wax layer in the blend is often achieved by tobacco selection and by using diluents such as RTS, expanded tobacco, and tobacco ribs and stems.

A number of efforts have been directed toward the addition of chemicals to the blend, a process which gives rise to agents capable of inhibiting pyroformation of PAH. These studies have often been successful; however, they are primarily of academic interest since the addition of chemicals can give rise to new toxic agents.

As discussed before, many of the laboratory methods for the reduction of the toxicity of cigarette smoke have found application in the commercial cigarette. Today most U.S. cigarette blends contain tobacco stems, RTS (>10 percent), and expanded tobacco.

As a consequence of the use of different tobacco blends, the nitrate content during the last 15 years has risen from about 0.5 percent to more than 1 percent. It has not been determined if an increase in

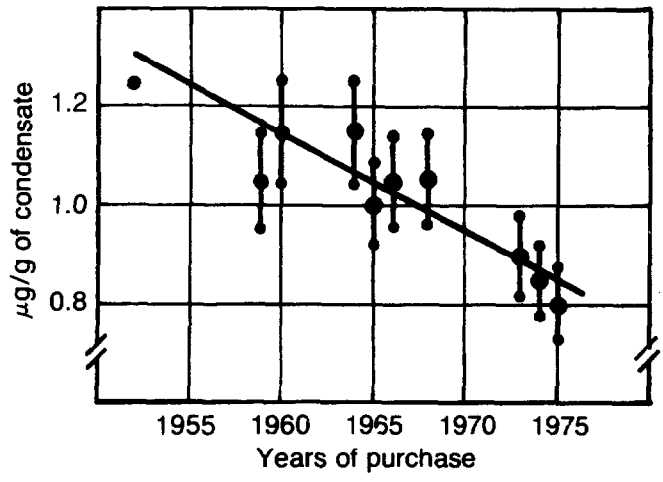

FIGURE 17.—Benzo(a) pyrene in the smoke condensate of a leading U.S. nonfilter cigarette.
SOURCE: Weber, K.H. (*41*).

nitrosamines has accompanied the increase in nitrate content. The result is that the content of PAH in the smoke of commercial cigarettes has significantly decreased during the last 25 years, as shown by the decrease of BαP in the smoke of a leading U.S. nonfilter cigarette in that period (Figure 17). Accordingly, the carcinogenicity of the tar of the same cigarette on mouse skin has significantly decreased over the years.

Nonvolatile N-Nitrosamines

As discussed earlier, about half of the tobacco-specific N-nitrosamines, NNN, NNK, and NAtB (Figure 3), in the smoke of U.S. cigarettes transfers directly from the tobacco into the smoke. In the leaf these carcinogenic nitrosamines are formed during curing and fermentation. It appears possible that they can be reduced in processed tobacco by specific bacteria, i.e., by pathways similar to those affecting nicotine reduction by bacteria (*19*). The reduction of the tobacco-specific nitrosamines in the smoke by selective filtration is not feasible and other methods for their reduction have not been reported thus far.

In the case of the carcinogenic N-nitrosodiethanolamine, the replacement of the precursor (diethanolamine) by another solubilizing agent for maleic hydrazide, the sucker growth inhibitor, is strongly suggested. For example, the potassium salt of maleic hydrazide would be more desirable.

Polonium-210

During smoking, Po^{210} is partially transferred from the tobacco into the mainstream smoke (*20*). Since a major portion of Po^{210} in U.S. tobaccos originates from the phosphate fertilizer (*36*), efforts should be continued to eliminate the use of fertilizers containing Po^{210}. A more effective way to reduce or remove Po^{210} and Pb^{210} is through the homogenized leaf-curing extraction process after harvesting. A gradual reduction of Po^{210} in tobacco is also expected to occur during the next decade with the decrease of airborne Po^{210}. Smoke filtration also removes radioactive particulates.

Summary

A number of methods have led to reduction of tar and of toxic and tumorigenic agents in the smoke of cigarettes. Table 26 lists the approaches that have led to the reduction of the ciliatoxicity and to selective reduction of the carcinogenicity and tumor-promoting activity of the smoke of experimental cigarettes. As mentioned repeatedly, many of these methods have already been incorporated in the modified blended U.S. cigarette of today.

TABLE 26.—Reduction of biological activity of cigarette smoke*

Method	CO	Cilia Toxicity	"Tar"	Nicotine	BaP	Selective Biological Reduction		Remarks
						Carcino-genicity	Tumor Promoters	
Agricultural Aspects								
Tobacco Varieties (Bright-Burley)	±	±	+	+	+	+	+	
New Tobacco Cultivars	?	+	+	+	+	?	?	
Leaf Position	+	+	+	+	+	?	?	Lowest stalk position; highest reduction
Selection by NO_3	+	±	+	+	+	+	?	
Tobacco Processing								
Extraction:								
Organic Solvents	±	±	+	+	+	+	?	Only of academic interest
Cut	±	±	±	±	±	±?	?	
Stems		+	+	+	-	++	++	
Reconstituted Tobacco Sheets (RTS)**	±	+	+	+	+	+	±	Some RTS give high CO
Reconstituted Tobacco Sheets (Paper Process)	±	+	++	+	+	++	?	
Expanded Tobacco	+	+?	++	++	++	±?	±	
Cigarette Production								
Porosity of Paper	++	+	+	+	+	±	?	
Perforated Filters	++	+	+	+	+	±	?	
Cellulose Acetate Filters	±	±	+	+	+	±	±	
Charcoal Filter***	±	++	+	+	+	+	±	
Additives: NO_3	±	-	+	+	+	+	±	Only of academic interest
Tobacco Substitutes	±	+	++	++	+	++	+	

*Reductions: ++ ≥50%, + significant; ± insignificant; ±? questionable; - increase; ? unknown.
**Data given for reconstituted tobacco sheets relate to those not made by the paper process.
***Reductions of "tar," nicotine, and BaP are in general greater with cellulose acetate filters than with charcoal filters.
SOURCE: Wynder, E.L. (42)

Reductions of the Toxic Activity of Cigarette Smoke: References

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Future Considerations

Research as described in the previous sections of this chapter has led to extensive scientific knowledge of the hazardous constituents of tobacco smoke and the association between tobacco usage and disease incidence. Additional research in several areas is warranted, however, to expand and refine this knowledge and to address challenging new problems that have been identified during previous research efforts.

In particular, of the more than 2,000 chemicals that have already been identified in tobacco smoke, relatively little is known about their metabolism and deposition within the human smoker. In addition to the effects of such chemicals individually, their synergistic effects must also be investigated. Furthermore, it is premature to infer that all carcinogens, co-carcinogens, and promotors in tobacco smoke have been identified.

Further research is also required for a better understanding of the role of smoke components and their metabolites on specific organ systems and in order to define more clearly the association between tobacco usage and disease incidence. Related to this type of inquiry is the investigation of how behavioral aspects of tobacco usage (particularly the frequency and depth of inhalation) influence the biochemical and physiological effects of pyrolyzed tobacco products on the human smoker. In conjunction with a better understanding of these issues, insights into the physiological alterations effected by smoke components such as nicotine, flavor additives, and other pyrolysis products may lead to further efforts to identify feasible pharmacologic intervention techniques to facilitate smoking cessation.

Concomitant with developing the kinds of information referred to above is the need for further identification of the precursors of pyrolized smoke components in the tobacco leaf itself. This, in turn, will guide agronomists and processors in controlling the levels of selected precursors in tobacco products. With the addition of selected physical characteristics, such as the type and porosity of wrappers and the materials used for filters, tobacco products can be produced that yield less toxic smoke.

The evidence is overwhelming that tobacco smoke is hazardous to the user; there is no scientific basis for asserting that non-toxic tobacco smoke is feasible. However, the potential for reducing the toxicity of tobacco smoke is indeed feasible, particularly within the research areas discussed above.

15. BIOLOGICAL INFLUENCES ON CIGARETTE SMOKING.

National Institute on Drug Abuse

PART II

THE BEHAVIORAL ASPECTS OF SMOKING

CONTENTS

Introduction 5

Chemistry and Biochemistry of Tobacco Smoke 5
- Carbon Monoxide 6
- Tar 7
- Nicotine 7

Metabolism and Fate of Tobacco in the Body 9

Predisposing Factors 9
- Genetic 9
- Endocrinological 10

Acute Effects of Tobacco and its Constituents Upon Establishment of Smoking 11
- Central Nervous System 11
- Cardiovascular System 12

Maintenance of the Smoking Habit 13
- Tolerance 13
  - Nicotine 14
  - Carbon Monoxide 15
  - Tar 15
- Metabolism 16
  - Nicotine 16
  - Carbon Monoxide 17
  - Tar 17
- Dependence 17

Physiological Effects of Tobacco and Its Constituents in the Maintenance of Smoking 18
- Central Nervous System 18
- Cardiovascular System 19
- Endocrinological System 20

Cessation of the Smoking Habit 20
- Early Effects of Cessation 20
- Long Term Effects of Cessation 22
  - Cardiovascular System 23

Endocrinological System 23
Other Effects 24
Dependence 24
Time Course and Duration 26
Degree of Deprivation 27
Gradual Reduction and Chronic Withdrawal 27
Other Factors Possibly Affecting the Abstinence Syndrome 27
Techniques for Measuring Tobacco Usage 29
Urine 29
Blood 29
Breath 30
Saliva 30
Verbal 31

References 32

LIST OF TABLES

Table 1.—Cigarette smoke: gas phase components 6

Table 2.—Cigarette smoke: particulate phase components 6

Introduction

The present chapter reviews current knowledge concerning the biological, biochemical, and physiological correlates of the smoking habit over the three stages of its development. These are respectively: establishment, maintenance, and cessation of the behavior. While there is overlap in each of these stages, one can conceptually divide the process and evaluate from a biological perspective the metabolism and fate of the major constituents of tobacco, the role of nicotine, dependence liability and tolerance associated with the smoking habit, and its physiological correlates. Recommendations for new research initiatives are included where appropriate throughout the text.

Chemistry and Biochemistry of Tobacco Smoke

Cigarette smoke contains a number of compounds that may act as pharmacological reinforcers and facilitate establishment of the smoking habit. Although it is difficult for a psychopharmacologist to ignore the possibility, indeed the probability or certainty, that the chemical composition of cigarette smoke is of vital importance in explaining smoking behavior, there are behavioral scientists who totally ignore chemistry. They focus instead upon the fact that smoking is initiated by peer pressure, and some have expressed the view that oral and manual satisfaction is all that is necessary to maintain the habit. Although it may be inappropriate to go to the opposite extreme and deny the importance of psychological factors in the establishment of the smoking habit, there is much direct evidence that cigarette smoking necessarily involves tobacco and probably nicotine. Cigarettes made of nontobacco materials such as lettuce or cubebs are not popular. The evidence that nicotine is a vital ingredient is somewhat more circumstantial.

A pack-a-day smoker takes more than 50,000 puffs per year and each puff delivers a rich assortment of chemicals into the lungs and bloodstream. Each puff stamps in the habit a little more and augments the establishment of secondary reinforcers, such as the sight and smell of cigarettes, the lighting procedure, and the milieu and context of a meal with a cup of coffee or a cocktail. It would be surprising if chemical factors were not involved in these pleasurable experiences. It is not surprising that such an overlearned habit surrounded by secondary reinforcers is difficult to extinguish.

The possible candidates for reinforcing pharmacological agents in the establishment of the smoking habit are shown in Tables 1 and 2 (*118*). Although nicotine is the most popular suspect for the reinforcing agent in tobacco, there are other possibilities. Tar and carbon monoxide are the two most likely contenders.

TABLE 1.—Cigarette smoke: gas phase components (μg/cigarette*)

Carbon monoxide	13,400
Carbon dioxide	50,600
Ammonia	80
Hydrogen cyanide (hydrocyanic acid)**	240
Isoprene (2-Me-1,3 butadiene)	582
Acetaldehyde	770
Acrolein (2-propenal)	84
Toluene	108
N-Nitrosodimethylamine	0.08
N-Nitrosomethylethylamine	0.03
Hydrazine	0.03
Nitromethane	0.5
Nitroethane	1.1
Nitrobenzene	25
Acetone	578
Benzene	67

* 85 mm non-filter, blended cigarette (U.S.)
** Gas phase portion only (74 μg/cig. in particulate phase)
SOURCE: Schmeltz, I. (*118*).

TABLE 2.—Cigarette smoke: particulate phase components (μg/cigarette)

TPM* wet	31,500
dry	27,900
FTC**	26,100
Nicotine	1,800
Phenol	86.4
o-Cresol	20.4
m- and *p*-Cresol	49.5
2,4 Dimethylphenol	9.0
p-Ethylphenol	18.2
β-Naphthylamine	0.028
N-Nitrosonornicotine	0.14
Carbazole	1.0
N-Methylcarbazole	0.23
Indole	14
N-Methylindole	0.42
Benz(*a*)anthracene	0.044
Benzo(*a*)pyrene	0.025
Fluorene	0.42
Fluoranthene	0.26
Chrysene	0.04
DDD	1.75
DDT	0.77
4,4′-Dichlorostilbene	1.73

* U.S. cigarette, 85 mm, without filter tip, 1968
** TPM-FTC = TPM-H_2O-nicotine
SOURCE: Schmeltz, I. (*118*).

Carbon Monoxide

After nicotine, the substance in cigarette smoke with the most

pronounced acute pharmacological action is carbon monoxide (CO). Cigarette smoke contains 1 to 5 percent CO, or 10,000 to 50,000 parts per million (ppm). Carbon monoxide impairs the oxygen-carrying capacity of the blood and may impair functioning of the nervous system. It appears to pose a threat, both acutely and chronically, to the functioning of those with cardiovascular disease. Indeed, it is thought by some (*128*) that the carbon monoxide in cigarette smoke is partially responsible for the increased risk of myocardial infarction and stroke in cigarette smokers. The combination of nicotine, with its catecholamine releasing properties, and carbon monoxide in the blood of smokers may enhance cardiovascular risk.

Little evidence exists to support the hypothesis that carbon monoxide is the reinforcing agent in establishing the smoking habit, although it may interact with nicotine. Quite possibly carbon monoxide may deter a few smokers from establishing the smoking habit because it may induce headaches which would deter further smoking. Other forms of tobacco (snuff and chewing tobacco) that have been used through the ages do not produce carbon monoxide.

Tar

Tar, the particulate phase of cigarette smoke, is also of importance in the establishment of the smoking habit. The possibility that tar may be reinforcing is not so easily disproved because the tar and nicotine content of cigarettes tend to co-vary. One study in which the tar and nicotine were dissociated and varied (*38*) showed that the number of cigarettes smoked was related to the nicotine content but not to the tar. There were indications that there may be an interaction between tar and nicotine. For example, nicotine strongly influenced strength ratings in the expected direction, while high tar cigarettes were actually perceived as milder than low tar. The results are consistent with the hypothesis that people smoke to obtain nicotine, but it would be important to extend and confirm these findings with a wider range of tar and nicotine content.

Nicotine

Nicotine has been proposed as the primary incentive in smoking (*63*) and may be instrumental in the establishment of the smoking habit. Whether or not it is the only reinforcing agent, it is still the most powerful pharmacological agent in cigarette smoke. Nicotine is rapidly extracted, enters the pulmonary circulation, is pumped to the aorta where it stimulates the aortic and carotid chemoreceptors, and may produce reflex stimulation of the respiratory and cardiovascular centers in the brain stem.

Within one circulation period, one fourth of the inhaled nicotine passes through the brain capillaries and, since it is highly permeable to the blood brain barrier (*99*), passes promptly into the brain. Once in the

brain, nicotine stimulates nicotine receptors. It also releases various biogenic amines, including the catecholamines and possibly 5-hydroxytryptamine. It may also stimulate some as yet unidentified receptors. It stimulates the emetic chemoreceptor trigger zone in the medulla and, in novices or in large doses, it causes nausea and vomiting. A variety of hypothalamic and pituitary hormones are stimulated by nicotine (*143*). The effects of nicotine on associative centers in the brain are still unexplored but may be of extreme importance in explaining its use and desirability during initiation of the smoking habit. Studies from a number of laboratories indicate that nicotine can have a facilitating effect upon learning and memory in animals (*84*), and possibly in humans (*2*).

The other three-fourths of the inhaled nicotine is delivered to the rest of the body and acts wherever there are nicotinic sites. Thus it stimulates autonomic ganglia with, for example, activation of the gastrointestinal tract. By the same mechanism, it releases epinephrine from the adrenal gland with all the "fight or flight" reactions that this hormone can produce, including mydriasis, tachycardia, vasoconstriction, bronchiolar dilitation, decrease in gastrointestinal motility (though this is generally successfully overcome by nicotinic ganglionic stimulation), and glycogenolysis. It also produces a rise in free fatty acids in the blood, and it can release catecholamines such as norepinephrine from nerve endings and chromaffin cells through the body. These diffuse physiological changes may contribute to increased arousal and thus be important corollaries in the establishment of the smoking habit.

Much of the evidence for the role of nicotine as the primary reinforcer in cigarette smoke is circumstantial. Smokers prefer cigarettes with nicotine than without (*40*), though they will smoke nicotine-free cigarettes.

Cigarettes with a nicotine content of less than 0.3 mg/cig do not do well on the market but recently have been increasing in popularity. Generally, these are smoked by individuals who are trying to cut down or somehow diminish the harmful effects of smoking. Tobacco-free cigarettes are doomed to oblivion almost from the start. Lettuce cigarettes had a brief vogue in the United States, but the two companies producing the two different brands on the market went bankrupt.

It is important to note that low or no-nicotine cigarettes allow their smokers to go through all the motions of smoking. Lighting, handling, and puffing can be the same as with usual cigarettes, so the opportunity for visual, olfactory, and oral gratification is present. It is the rare smoker, however, who continues to smoke cigarettes lacking nicotine for any length of time when the more popular high nicotine cigarettes are available. The most likely explanation for this preference is that nicotine is reinforcing.

Metabolism and Fate of Tobacco in the Body

There is little data relating metabolism and fate of tobacco to the establishment of the smoking habit in adolescence. Differences, however, have been found in the metabolism of tobacco in adult nonsmokers and smokers. Beckett and Triggs (*8*) administered nicotine to smokers and nonsmokers and measured urinary nicotine content. The nicotine content in urine from smokers (55 to 70 percent) was consistently higher than from nonsmokers (25 to 50 percent). It would be useful to do enzyme studies in a large sample of adolescent and preadolescent subjects to determine whether chemical profiles might help predict who will take up smoking and who will not. Also, if there are biological deterrents to smoking, it would be useful to find them.

Predisposing Factors

Genetic

Relatively little is known about biological factors in the initiation of the smoking habit. Many studies that have implicated biological factors in the initiation of smoking behavior attribute the behavior to a genetic predisposition. Initial twin studies by R. A. Fisher (*33*) led him to hypothesize that genotype was a significant variable in smoking behavior. In his survey of twins from Germany and England, he reported that monozygotic twins were more concordant in their smoking behavior than dizygotic twins.

Eysenck (*30*) has measured personality variables and has concluded that smoking behavior is related to the extroversion-introversion dimensions of personality. Eysenck's theory assumes that differences in these dimensions of personality are for the most part determined by hereditary factors. He presents evidence indicating that monozygotic twins are more alike on these dimensions than dizygotic twins, and that cigarette smoking is associated with the extroversion dimension of personality. These data have in part formed the basis for the common genotype hypothesis. This hypothesis states that tobacco smoking and lung cancer (and in the theory of Eysenck, personality factors) are due to a common genetic mechanism (*76*). Subsequent analysis of twin studies have supported (*18, 119*) and denied (*113, 139*) a significant genetic influence on smoking behavior. However, Cederlof, et al. (*19*) recently published an extensive review of the data from the Swedish twin registry and concluded that "the constitutional hypothesis as advanced by Fisher and still supported by a few, has here been tested in twin studies. The results from the Swedish monozygotic twin series speak strongly against this constitutional hypothesis." The Chapter on Mortality in this report contains a more complete discussion of this topic.

In general, studies from which inferences about genetic mechanisms and smoking have been made are subject to many of the pitfalls

associated with survey-type research. Studies of twins are among the most popular means of assessing genetic factors (*14*). Unfortunately, the small number of subjects used in twin studies (particularly monozygotic) has limited the inferences that can be made about genetic mechanisms. An additional confounder not controlled in twin studies is the prenatal environment. The prenatal environment for monozygotic twins is likely to be more similar (i.e., twin positions, common circulatory factors, etc.) than for dizygotic twins (*88*). Further progress in this area will depend on more exhaustive and sophisticated methods of analysis.

Endocrinological

The importance of endocrine factors in the establishment of the smoking habit has not been explored. There is abundant evidence that hormonal changes in puberty occur at about the same time that individuals start smoking. Retrospective studies indicate that teenage smokers are more outgoing, self-confident, and rebellious toward established authority than their nonsmoking counterparts.

The acute endocrine changes associated with cigarette smoking are difficult to interpret because of non-specific stress factors which may accompany smoking. Winternitz and Quillen (*149*) measured ACTH and growth hormone levels in nonsmokers after smoking two cigarettes. There was a rapid increase in the plasma levels of both hormones, but the authors were unable to determine if the effect was due to the tobacco smoke or to the stress created by smoking. The subjects developed nausea, became pale, and started sweating. In chronic smokers a sharp rise in plasma cortisol was observed after two cigarettes and was maintained for several hours. Growth hormone levels peaked at 1 hour and fell back to control levels during the second hour of measurement. No significant changes were found in LH, FSH, TRH, and testosterone levels.

One of the most frequently demonstrated endocrine effects of nicotine is the stimulation of vasopressin release from the supraoptic nucleus (*5, 46, 110*). Robinson and his colleagues have shown in humans that nicotine stimulates the release of a neurophysin associated with vasopressin secretion. A second estrogen-stimulated neurophysin was not affected by nicotine treatment.

In a similar study, Hayward and Pavasuthipaisit (*46*) measured plasma vasopressin levels in adult female monkeys after intravenous infusion of nicotine (100 μg/lkg/min). A significant increase in circulating vaspressin levels was measured that could, in part, be abolished by pre-treatment with promethazine and diphenhydramine. The association between endocrinological responses and smoking is not clear, however. That smoking *causes* such responses has been established, but it would be important to determine whether these responses in turn reinforce further smoking.

Acute Effects of Tobacco and Its Constituents Upon Establishment of Smoking

Central Nervous System

It is clear that tobacco has reinforcing properties that motivate its users to continue smoking even when they are aware of the possible health consequences. Nicotine appears to be the chemical in tobacco that is most likely responsible for these effects (*63*). When the nicotine and tar content are varied independently, it is the nicotine content that is correlated with ratings of strength and satisfaction (*39*). Numerous investigators have shown that nicotine will release norepinephrine from postganglionic sympathetic sites, acetylcholine from postganglionic parasympathetic sites, and epinephrine from the adrenal medulla. However, the primary sites of reinforcement appear to be in the central nervous system. Oldendorf (*99*) has demonstrated that nicotine readily crosses the blood-brain barrier. Stolerman, et al. (*127*) administered mecamylamine, a central nicotine antagonist, to smokers and observed an increase in cigarette consumption. This change was presumably an attempt to overcome the blockade. Further, when the peripheral antagonist, pentolinium, was administered, no change in cigarette consumption was noted. These data are supported by animal studies indicating that rats trained to discriminate nicotine from saline do not generalize the response to similar drugs (*116*). In a related study, Hirschhorn and Rosecrans (*51*) reported that mecamylamine abolished an established nicotine discriminative response.

An important central nervous system effect of nicotine is its ability to modulate arousal levels. The cortical EEG has been used by many investigators as an index of changes in arousal processes (*58, 66, 135*). When smokers are deprived of tobacco for short periods of time, there is an increase in lower-frequency and high-amplitude waveforms in their EEG, thus indicating a possible state of "hypoarousal." Interpretation of these studies has proved difficult because adequate control groups were not employed. It is possible that the process of inhaling in a manner that simulates smoking will elicit the same EEG changes as smoking a cigarette.

The study of Kales, et al. (*66*) in some ways tempers this criticism in that it demonstrated differences in sleep patterns between nondeprived and deprived smoking conditions. During deprivation, smokers spent more time in REM sleep than during nondeprived states. This result could also be due to nonspecific stress.

Research has shown that animals may self-administer nicotine. For example, Pradhan and Bowling (*106*) studied the effects of intraperitoneal administration of nicotine on self-stimulation in rats. The baseline rate of self-stimulation varied as a function of electrode placement, current intensities, and time spent lever-pressing. At high baseline levels of self-stimulation, nicotine enhanced the rate of stimulation.

These data are consistent with other studies that demonstrate that drug effects are largely dependent upon baseline levels of self-stimulation. In a somewhat different approach, Yanagita (*153*) has studied the reinforcing properties of nicotine by demonstrating that monkeys will self-administer nicotine on a regular basis when given the opportunity. An earlier study by Deneau and Inoki (*23*) presented similar results.

There are very few studies in which nicotine alone has been administered to man in an attempt to produce reinforcement (*64, 65, 80*). Johnston injected himself and other volunteers with nicotine and obtained clear evidence of reinforcement. These unique studies were uncontrolled for suggestion, however. There were three studies in which nicotine was given either by ingestion or intravenously, and in all three, it was incapable of completely suppressing smoking, though it usually had some suppressant effect. Indeed, in the experiment by Kumar, et al. (*75*), there was no discernible effect of a rapid intravenous infusion of 1.17 mg of nicotine. Subjects went on puffing their cigarettes just as they did with an equivalent injection of placebo, and there was no delay in latency to the first puff.

The results are disturbing to proponents of the nicotine hypothesis of smoking. It is clear that the intravenous infusions had no effect on the subsequent puffing of cigarettes, whereas the cigarettes smoked immediately preceding the test session had a marked effect both on latency to the first puff and on the rate and volume of puffing. Perhaps the nicotine delivered to the blood and brain were not equivalent in the two conditions. Perhaps the intravenous dose should have been higher; it might have been swamped by the fact that *ad lib* smoking was allowed during the intravenous administration of nicotine. Clearly more research is needed to clarify these results.

If it could be established that central nervous system effects of smoking were reinforcing, it would be important to study these actions in novices.

Cardiovascular System

Before he takes his first cigarette, the novice is not likely to be aware of his cardiovascular system. The first cigarette, however, may have a very profound effect upon the heart and blood vessels of a nonsmoker. The tachycardia may be perceived either as a pleasant or unpleasant sensation. The cardiovascular changes associated with tobacco intake resemble the effects elicited by nicotine alone. Both sympathetic and parasympathetic ganglia are stimulated by low concentrations of nicotine, and nicotine can have sympathomimetic effects by releasing epinephrine and norepinephrine from chromaffin cells in the adrenal medulla, heart, blood vessels, and skin (*139*,. Increases in heart rate (10 to 25 beats per minute), blood pressure (10 to 20 mm Hg systolic, 5 to 15 mm Hg diastolic) and cardiac output (0.5 $l/min/m^2$) typically occur in