both nonsmokers and smokers after smoking one or two cigarettes. In addition, digital blood flow and finger and toe temperature fall (*139, 151*).

The acute cardiovascular responses to tobacco and nicotine have been summarized in the Surgeon General's reports on the health consequences of smoking (*136, 138*). These reports list the following acute changes from smoking: increased (1) heart rate, (2) blood pressure, (3) cardiac output, (4) stroke volume, (5) velocity of contraction of the heart, (6) myocardial contractile force, (7) coronary blood flow, (8) myocardial oxygen consumption, (9) arrhythmia induction, and (10) electrocardiographic changes. These effects are assumed to be due to catecholamine release from the adrenal medulla, chromaffin tissue, or sympathetic nerve endings, and are similar to those obtained by sympathetic stimulation. They are to a considerable extent mediated by sympathetic excitation (*139*). These diverse cardiovascular changes may be a significant component in shifting the arousal continuum toward an optimum level for smokers. However, there are no controlled experiments that definitely rule them in or out as contributors to the reinforcing properties of cigarettes.

Maintenance of the Smoking Habit

The biological factors which can be implicated in the maintenance of smoking have, by no means, been thoroughly investigated. A great deal is known about the *harmful* biological consequences of smoking, but very little about the *beneficial* effects. It is evident that some component or components in tobacco and tobacco smoke must be reinforcing, but these have not been unequivocally identified. As noted earlier, the possible candidates for reinforcing agents can be seen in the two tables (Tables 1 and 2) from Schmeltz and Hoffman (*118*). The leading contender is nicotine because it is clearly a powerful pharmacological substance and is administered in ways consistent with its action as a reinforcer. There are, however, some inconsistencies in the literature. Yanagita (*153*) has reported low levels of nicotine self-administration in monkeys and rats respectively, while Russell, et al. (*111*) report a lack of evidence for self-administration in man, as well as in other animals. The present discussion focuses upon tolerance to tobacco and its constituents, the metabolism and fate of the constituents, and their physiological effects as they relate to the maintenance of the smoking habit.

Tolerance

By definition, tolerance is manifested by a decreasing response to repeated administration of the same dose of a drug, or by the requirement for increasing doses in order to elicit the same response. Martin (*81*), Jaffe and Sharpless (*61*), and others have proposed models

which imply that dependence and tolerance are based upon identical mechanisms. It is difficult to think of an example of a drug to which dependence occurs that does not also involve tolerance. On the other hand, tolerance may occur without dependence (e.g., phenothiazine, antihistamines).

Three kinds of tolerance are apt to occur with tobacco use as with other types of drug use: drug dispositional or metabolic tolerance, tissue or pharmacodynamic tolerance, and behavioral tolerance. The first refers to methods that the body uses to eliminate or to deactivate the drug. For most chemicals derived from tobacco, the liver is the organ most heavily responsible for detoxifying or transforming them into inactive and eliminable forms. The kidney is also important, especially for alkaloids whose water solubility varies with the pH of the solution. The second kind of tolerance refers to changes in the ability of receptors to be activated by the drug at its final site of action. The third type refers to the way in which the subject using the drug changes his behavior to adapt to the effects which the drug repeatedly produces.

Of the compounds contained in tobacco and tobacco smoke (*118*), three are of primary biological importance: tar, carbon monoxide, and nicotine. There is evidence that tolerance can develop to the effects of each of these, although their interaction has scarcely been studied. While there is evidence that tolerance may develop to other components such as acetone and phenol, it is unclear how much they contribute to the pharmacological actions of cigarettes.

Nicotine

Stolerman, et al. (*126*) examined the interaction between pairs of injections of nicotine which varied both in dose and in interval. Two measures of spontaneous locomotor activity of rats in a T-maze were taken: rears and entries. After a single treatment with nicotine, acute tolerance developed as indicated by a shift of the dose-response curve. The dose of nicotine required to produce a given decrement in activity was multiplied by a factor of about 2.4 when a delay of 2 hours was taken between the two injections. When the initial dose was varied, it was found that there was an optimal level for producing tolerance. Higher doses were less effective. An explanation for the relative ineffectiveness of the higher doses in producing tolerance is not available. A general debilitating effect of pretreatment with large doses does not seem to explain it, as rats given a saline challenge exhibited normal motor activity. Perhaps the debilitating effects of a large pretreatment dose and a challenge somehow summa .e.

Carbon Monoxide

Levels of carbon monoxide achieved in the human body following cigarette smoking increase levels of carboxyhemoglobin. These chronically high levels of carboxyhemoglobin found in smokers can induce polycythemia by increasing hemoglobin levels. These compensatory changes enable the smoker to tolerate increased carbon monoxide levels and to cope with the oxygen deficit produced by cigarettes.

Tar

Tar is defined as the total particulate matter (TPM) collected by a Cambridge filter after subtracting moisture and nicotine. The polycyclic aromatic hydrocarbons are generally blamed for a substantial portion of the carcinogenic activity of tar. They are also powerful enzyme inducers and are undoubtedly responsible for much of the tolerance to themselves and a variety of other compounds produced by smoking. The tar content of cigarette smoke for all brands is determined yearly by the Federal Trade Commission which publishes a listing, along with nicotine content. Tar and nicotine tend to co-vary and thus their effects may be confounded. Obviously, tar is obtained in the smoke from pipes and cigars but not from chewing tobacco and snuff. The latter do not deliver pyrolysis products, such as carbon monoxide, and may thus be somewhat safer. Because the hepatic microsomal enzyme formation is induced by a number of carcinogens in the tar fraction of cigarette smoke, including benzopyrene (*96*), smokers are rendered tolerant to both the therapeutic and toxic effects of a wide variety of drugs (*129*). Even the enzymes in platelets are activated (*53*).

The phenomenon of tolerance to the effects of tobacco products has been clearly demonstrated in both humans and animals. As might be expected, most of the emphasis has focused upon nicotine, but carbon monoxide and tar components also play an important role. As with all other drugs, tolerance varies with subjects and functions. Certain invertebrate forms which feed on the tobacco plant have a high genetically determined tolerance. It is reasonable to assume that even in humans some of the variance in response to tobacco is innately determined and may account for some of the high concordance in smoking behavior seen in identical twins. Other forms of tolerance are clearly the result of experience and develop after exposure to tobacco products. Much more research needs to be done to determine the degree of tolerance which develops in different physiological and psychological functions after tobacco use. For example, it is evident that even in heavy smokers of long duration the heart rate speeds up after each cigarette. On the other hand, nausea and vomiting diminish and disappear with continuing moderate use of cigarettes. It would be very informative indeed to know what changes take place at the

putative sites of action of nicotine with chronic use. Do nicotinic synapses at ganglia change in the same way as nicotinic synapses in the brain? Do carbon monoxide and tar constituents have any action on these components or on enzyme systems elsewhere in the body? Answers to these questions will enable us to understand better the physiological basis of the smoking habit.

Tolerance to the effects of cigarette smoke was noted in dogs given cigarette smoke via tracheostomy (*44*). At the beginning of the study the smoke was aversive, but with the passage of time, animals exhibited tail wagging and improved cooperation. In a careful study, Stolerman, et al. (*127*) showed the development of both acute and chronic tolerance in rats. Nicotine administered intraperitoneally to experimentally naive rats depressed activity in a Y-shaped runway in a dose-related manner. After a single intraperitoneal dose of nicotine, acute tolerance to the depressant action of a second dose developed with a definite time course. This became maximal after 2 hours and wore off after about 8 hours. Repeated intraperitoneal doses of nicotine (three times daily for 8 days) elicited chronic tolerance which persisted for at least 90 days after the end of regular treatment with the drug. Tolerance was also produced when nicotine was administered in rats' drinking water and through reservoirs implanted subcutaneously. It appears, then, that tolerance to nicotine in rats can develop quickly, may be easily measured, and persists for prolonged periods after withdrawal. In these experiments, rapid withdrawal of nicotine did not produce the signs of illness which morphine withdrawal regularly produced. The existence of prolonged tolerance to nicotine in rats suggests that the same phenomenon might exist in man. If tolerance to the unpleasant effects of nicotine, such as nausea, developed more rapidly and persisted longer, it might facilitate relapse to tobacco use.

Metabolism

Nicotine

Tne metabolic fate of 1 mg of nicotine base injected intravenously in humans (actually as nicotine hydrogen tartrate) was intensively investigated by Beckett, et al (*7*). They found that smokers excrete nicotine significantly faster than nonsmokers. None of the smokers reported any nausea from the nicotine injections, but this was reported in varying degrees by all nonsmokers. Haines, et al. (*42*) reported that the plasma concentrations of nicotine were actually higher in smokers than in nonsmokers 1 minute after smoking, but these results were confounded by the fact that nonsmokers were instructed to smoke cigarettes. Obviously smokers were able to inhale more effectively than nonsmokers, in part because they had acquired tolerance to the aversive effects of cigarette smoke on the respiratory passages. Indeed, some of the tolerance that smokers show to cigarette smoke

may be correlated with diminished function of the respiratory epithelium and possible depression of taste and smell (*70*). The proposition that heavy smokers adjust their plasma nicotine levels is compatible with the observation that regular smokers commonly consume about 20 to 30 cigarettes during the smoking day (approximately one every 30 to 40 minutes) and that the biological half life of nicotine in humans is approximately 20 to 30 minutes (*57, 111*). While studies with intravenous nicotine (*80*) show changes in smoking rate apparently due to nicotine concentration in the blood, studies using nicotine gum (*73*) did not show the same effects as intravenous nicotine. It is postulated that the nicotine derived from the gum is absorbed in the intestine and sent to the liver directly via the portal and is there metabolized; therefore less nicotine enters the systemic circulation. Most investigations of smoking rates indicate that much more than plasma nicotine level regulation is involved.

Carbon Monoxide

The metabolism of carbon monoxide involves both the exhalation of the substance from the lungs and a compensatory increased hematocrit to increase oxygen capacity. The former is slowed by the high affinity of carbon monoxide for hemoglobin, and the latter's rate is limited by the process of hematopoiesis. Carboxyhemoglobin has a half life in the body of at least 3 to 4 hours (*137*). It is not known whether the metabolism of carbon monoxide plays a physiological role in the maintenance of the smoking habit.

Tar

Some examples of the effects of induction of microsomal enzymes are cited by Hunter and Chasseaud (*54*). Aryl hydrocarbon hydroxylase is regularly induced by smoking. Benzopyrene hydroxylase and aminozao dye N-methylase were higher in the placentae of pregnant smoking women than in those of nonsmokers. Since tar induces the enzymes of its own metabolism, the smokers might be expected to continue to smoke so as to maintain the levels of tar in the blood, thereby maintaining the action of tar on the metabolism of toxic substances, as discussed above. Metabolism of benzodiazepines, propoxyphene, pentazocine and phenacetin is increased in smokers. Xanthines such as theophylline are also metabolized more quickly in smokers (*105*) and, by inference, so should caffeine be metabolized more quickly. Perhaps this is why heavy smokers drink more coffee than nonsmokers (*9*).

Dependence

Dependence may play an extremely important biological role in the maintenance of the smoking habit (*147*). The characterization of tobacco use as a dependence process raises the issue of tobacco

withdrawal. Thus, the subject of dependence is deferred to the section on cessation of the smoking habit to be discussed in conjunction with the acute effects of cessation and the abstinence syndrome.

Physiological Effects of Tobacco and Its Constituents in the Maintenance of Smoking

Although a great deal has been written in previous editions of the Surgeon General's Report on the untoward effects of smoking, very little has been said about the factors that might be responsible for the establishment and maintenance of the habit. In the past 15 years the public has been exposed to ample warnings about the dangers of smoking; nonetheless the incidence of smoking remains high. Therefore, it is important to consider both the evidence and hypotheses about why smoking is such a tenacious habit. The actions of cigarette smoke and its components upon the central nervous system, cardiovascular system, and endocrine system might give us a clue to the strength and persistence of the habit.

Central Nervous System

In their study of smokers, deprived smokers, and nonsmokers, Knott and Venables (*72*) showed that the deprived smoker is characterized by a "state of cortical hypo-excitation and that tobacco smoking increased cortical excitation to the level of the nonsmoker." Citing the findings that tobacco smoking improves efficiency, prevents deterioration of reaction time (*35*), and improves learning (*1, 3, 17*), they suggest "that individuals smoke to achieve this specific psychological state of increased vigilance and attention associated with alpha frequency."

Nelsen, et al. (*95*) studied the effects of nicotine administered (100 μg/kg) subcutaneously to rats. The rats had electrodes placed in the reticular formation which, when stimulated, blocked visual learning tasks. The nicotine attenuated the electrical stimulation and increased learning. The suggestion is made that the nicotine-induced limbic system activation antagonized the behavioral disruption.

In Carruthers' attempt to isolate the "rewarding centers" (*16*), he used a β-blocker, oxprenolol, to decrease epinephrine and norepinephrine associated with anxiety and smoking. The secondary effects of increased heart rate, blood pressure, and free fatty acids were blocked along with the systemic increase in catecholamines, and yet the satisfaction subjectively evaluated was unchanged. His conclusion was that there may be a hypothalamic norepinephrine release leading to pleasure. It is not clear whether the oxprenolol crosses the blood-brain barrier. The more conservative conclusion would be that heart rate, blood pressure, and free fatty acid increases might not be involved in the pleasure associated with smoking.

In addition to the learning studies mentioned above, recent studies add the following data. Stevens (*124*) studied 115 males on four learning tasks. His conclusion was that those who smoked more than 12 cigarettes per day did significantly less well than the nonsmokers and light smokers. Andersson and Hockey (*2*) showed that, in two groups of 24 female students who were habitual smokers, the group in a control, no-smoking condition showed immediate serial recall equivalent to that of the group allowed to smoke one cigarette. The group not smoking did perform better in incidental memory, such as remembering in which corner the words were presented. This suggested that the cigarette increased attentional selectivity during increased arousal. Elgerot (*28*) used three complex and two simple tests to determine differences between a 15-hour abstaining group and the same group after smoking freely. In the nonsmoking condition, they improved on complex tests but were unchanged with respect to simple tests. The interpretation is based on the performance-arousal curve: "According to the Yerkes-Dodson law, the optimal level for arousal is lower for complex than for simpler tests." The conclusion is that the combination of the task and the cigarette led to an arousal level too great for the complex tests. An alternative hypothesis is that the smokers were under-aroused and that the abstainers were anxious enough, but not too anxious. The second explanation would account for the finding, but it is not consistent with other authors. Elgerot (*28*) cites the following effects in habitual smokers: (1) decreased hand-steadiness (*36*), (2) improved simple and choice reaction times (*93*), (3) improved driving tasks demanding sustained performance (*48*), and (4) impaired short-term memory but favorable effects on consolidation (*1*). Some of these changes in arousal levels and functioning capacities may be of benefit to the smoker and may reinforce maintenance of the smoking habit.

Other effects of smoking on the nervous system may be positively reinforcing. Decreased acetylcholine axonal transport and synthesis in neurons (*49*) may lead to decreased GI motility and augment the sympathetic response in calming digestion. Other investigators have shown no basic differences in the basic taste sensations between smokers and nonsmokers (*83*).

Cardiovascular System

The most commonly reported acute changes in the cardiovascular system are the following: increase in plasma catecholamines (*4, 78*), increased heart rate (*4, 5, 78*), increased blood pressure (*4, 5*), vasoconstriction (*43, 94*), and increased carboxyhemoglobin (*4, 98*). It is conceivable that cardiovascular changes are associated with pleasant emotional experiences, although Carruther's (*16*) β-blocking experiment would not support this possibility. Possibly decreased peripheral blood flow (*43*) is a heat-conserving mechanism which may drive

individuals to smoke. The increased viscosity of the blood due to increased hematocrit (*140*) is of unknown benefit on a chronic basis.

Endocrinological System

Although there has been much recent research on endocrine effects of smoking, the role these play in the smoking habit has scarcely been examined. With the development of more refined and more economical techniques for measuring hormones and their actions, we can expect an acceleration of research in this area.

Hayward and Pavasuthipaisit (*46*) administered IV nicotine to monkeys, causing an increase of arginine vasopressin (AVP) without changes in plasma osmolarity. Husain, et al. (*55*) and Robinson (*109*) also demonstrated the release of AVP plus neurophysins in humans.

Cryer, et al. (*22*) demonstrated that growth hormones and cortisol are released by smoking and are unaffected by β-blockers. Both are involved in protein and carbohydrate metabolism. Perhaps their effect on plasma glucose helps reinforce the smoking habit. Similar results were found by others (*100, 141, 149*).

Perhaps a factor involved in maintenance of smoking is the increased lipolysis due to release of catecholamines and glucocorticoids. A common reason given for returning to smoking is weight gain (*150*).

Other endocrinological effects of nicotine include increased gastric HCl secretion (*24, 89*), decreased pancreatic bicarbonates and water secretion secondary to inhibition of secretin (*11, 12, 13, 25*), changes in placental hormones (*21, 122*), alteration in prostaglandin formation (*144*), and delayed LH surge in female rats (*85*). Also, it is known that in smokers there is decreased sperm quality and distribution (*117*). Smokers and nonsmokers do not seem to vary in LH, TSH, T4, and FSH (*149*), however.

Cessation of the Smoking Habit

Early Effects of Cessation

Cessation of smoking is associated with alterations in CNS, cardiovascular, and other physiological functions. Whether these are true "withdrawal" phenomena characterized by a rebound or merely a return to normal levels still remains to be determined. It is evident, however, that significant changes do occur.

A number of physiological changes have been observed on withdrawal from tobacco. Decreases in heart rate and diastolic blood pressure are observed as early as 6 hours after withdrawal (*91*). These changes persist for at least 3 days (*71*), (*146*) and perhaps for 30 (*37*). Decreased excretion of both adrenaline and norepinephrine (*92*) and various metabolic changes have also been observed (*37*).

These metabolic and peripheral effects, which are often associated with decreased arousal, have been supported by EEG studies showing increases in low-frequency activity (*135*) and alterations in cortical alpha frequencies (*72*). Ulett and Itil (*135*) recorded cortical EEG from heavy smokers (one pack of cigarettes per day) in an attempt to detect EEG changes associated with acute withdrawal. Baseline EEG measurements were obtained while the smokers engaged in their normal smoking pattern and were compared with data from the same individuals after they were deprived of tobacco for 24 hours. It was found that there was a significant increase in the low-frequency EEG bands (3-5-7 cycles/sec) during deprivation. This effect was readily reversed after the subjects smoked two cigarettes within a 5-minute period.

In a similar study, Knott and Venables (*72*) did a computer analysis of cortical alpha activity in male nonsmokers, smokers asked to abstain for a 13- to 15-hour period, and smokers who continued their normal pattern of smoking. Analysis of variance of pre-smoking alpha activity indicated the mean alpha frequency of the subjects in the deprived group was significantly lower (9.3 Hz) than in the nonsmoking group (10 Hz) and nondeprived group (9.9 Hz). When the deprived group smoked two cigarettes, the alpha frequency increased to the levels of the nonsmoker and smoker control groups. Thus, there is evidence for a rebound effect and a true withdrawal reaction. The data are interpreted as indicating that deprived smokers are in a state of cortical "hypo-excitation," and that smoking has the effect of increasing excitability to levels comparable to those found in non-smoking and nondeprived groups. Since all groups were equal on measures of extroversion, the authors hypothesize that they have described a true "smoking factor" rather than a difference due to personality. Alternatively, one could conclude from the same data that the results obtained are due to the removal of an arousal-producing drug from a group of people who are ordinarily hypo-aroused.

Numerous other physiological changes have been noted to occur after cessation of smoking. Ejrup (*27*) reports that weight gain is a common sequela to cessation. Although not generally observed, he reported that, in a number of patients, blisters in the mouth occurred along with constipation upon cessation of smoking. If the patients resumed smoking, the blisters disappeared.

Krumholz, et al. (*74*) have measured changes in cardiopulmonary function at rest and during exercise 3 and 6 weeks after cessation of smoking. All subjects had smoked more than one pack of cigarettes a day for at least 5 years. Changes during exercise were measured on the standard bicycle-ergometer test. Following 3 weeks of abstinence, heart rate, oxygen debt, and ratio of oxygen debt to total increase in oxygen uptake during exercise were significantly reduced. In addition, expiratory peak flow and D_L were significantly increased. Pulmonary

compliance increased after 3 weeks and continued to do so at 6 weeks. At 6 weeks, maximum voluntary ventilation and inspiratory reserve volume were increased and functional residual capacity was decreased.

Glauser and colleagues (*37, 38*) studied seven subjects before and 1 month after cessation of smoking. The following measures were found to have changed significantly: (1) body weight increased from a mean of 188 to 195 pounds, (2) body surface area increased from 2.03 to 2.05 m, (3) heart rate decreased from 60 to 57 beats per minute, (4) sugar levels (30 seconds after eating) fell from 137 to 123 mg percent, (5) protein-bound iodine decreased from 5.1 to 4.6 μg percent, (6) serum calcium decreased from 10.2 to 9.7 mg percent, and (7) oxygen consumption decreased from 283 to 260 ml of oxygen/min. The authors concluded that the metabolic change that follows cessation of smoking may be one important variable that causes an increase in weight.

Myrsten, et al. (*93*) have studied chronic smokers who smoked for 5 days, abstained for 5 days, and smoked for 5 additional days. Results from this group were compared with those from a nonabstaining group of smokers. A number of physiological differences were noted during the abstinence period. Adrenaline and noradrenaline excretion levels decreased, skin temperature increased, heart rate decreased, and hand steadiness improved.

Accompanying these objective changes in physiology and performance are subjectively reported changes in physical symptoms, arousal, and mood. These have been reported in studies of smokers sampled while actually undergoing withdrawal (*34, 41, 146*), as well as in retrospective studies of ex-smokers up to 14 years after cessation (*15, 34, 82, 103, 112, 131, 152*). Although the specific symptoms reported in each study differ, as does the percentage of abstinent smokers reporting each symptom, a consistent pattern of symptoms can still be discerned. Common among the physical symptoms reported are nausea, headache, constipation, diarrhea, and increased appetite (*41, 92, 146*). Also reported are disturbances of arousal, including drowsiness and fatigue, as well as insomnia and other sleep disturbances (*92, 152*). Inability to concentrate is a common complaint and is consistent with objective assessments of the concentration of smokers in abstinence (*46*). Thus, the objective changes reviewed above appear to be reflected in the subjective experience and self-reports of deprived smokers.

Long Term Effects of Cessation

Once a smoker gets past the initial 3- to 14-day withdrawal effects (*45, 59, 120*), what biological factors tend to encourage the now ex-smoker to continue abstinence? The factors opposing most ex-smokers' attempts to refrain seem to win out, since relapse is so frequent. In all cessation methods described, about two-thirds are able to attain some degree of abstinence for a short duration, but about half of these return to smoking in 1 to 2 years (*20, 68*). Is it the methodology of

cessation or the post-cessation factors which determine continuation of abstinence? Kasl (*69*) claims "there is evidence that smokers who stop spontaneously have a lower rate of relapse than those who seek help and participate in some sort of program." The effects of cessation on the central nervous system, cardiovascular system, and endocrine system which might encourage continued abstinence will be discussed along with some of the psychobehavioral components.

Cardiovascular System

When a smoker terminates his intake of tobacco, he reduces his risk in a number of cardiovascular diseases: coronary heart disease (*29, 50, 67, 123*), cerebrovascular accidents (*50*), recurrence of myocardial infarction (*29*), sudden death from CHD (*67, 123*), myocardial infarction (*123*), and complications of atherosclerosis (*101*). These reduced risks are measurable on populations, but what cardiovascular benefits of cessation exist to individuals? One report says that the subendothelial edema of small arterioles and vasa vasorum is secondary to the carbon monoxide of cigarettes and that this, including coronary arteries (*5*), tends to return to normal after 5 to 10 years of cessation. This might reinforce cessation, especially in ex-smokers with angina pectoris or other ischemic heart disease. Janzon (*62*), using venous occlusion plethysmography on the calf, found that after 8 to 9 weeks of cessation peripheral blood flow increased measurably, whereas the control group of continuing smokers actually decreased their peripheral blood flow. It is likely that this improvement of circulation would be accompanied by a sense of well-being and reinforce abstinence as time progressed. The decrease in heart rate and blood pressure (*52*), along with decreased catecholamines, may be a factor in continuing abstinence. Related to the cardiovascular benefits of cessation, it was found that peak-expiratory flow rates of 57 liters/min resulted (*90*), an increase which would be positively reinforcing, especially in active ex-smokers.

Endocrinological System

If the metabolic rate declines (*52*), the major effect would be increased weight, as has been noted by many (*34, 37, 82, 148*). This would tend to reinforce smoking in most people. But there may be some unseen benefit of decreased metabolism in those who are either able to maintain their weight or who are not self-conscious of weight gain.

In Pearson's study of theophylline metabolism (*102*), he found that smokers' half-life of theophylline was 4.2 hours while nonsmokers' was 7.1. Upon cessation, the normalization (toward 7.1) took 3 months to 2 years, implying that there may be induced enzymes in the smoker which do not readily normalize. This may be indicative of other metabolite-clearing processes and, because the normalization effect is gradual, may keep the ex-smoker in a "smoking" state so that he does

not "miss" this aspect of smoking. Is it possible that this kind of normalization is responsible for so many returning to smoking after 1 to 2 years (*20, 68*)? Another possible influence may be in sex hormonal levels. After 3 months there is improved quality of sperm motility and density as well as fertility (*117*).

Other Effects

Pederson and Lefcoe (*103*) used the Jackson Personality Inventory and a modification of the Reid-Ware Internal-External Control Scale and found no difference between smokers and successful ex-smokers. They point out that ex-smokers have usually tried to stop at least once and failed, have stopped for health reasons, have experienced cravings and discomfort, and have used substitutes. The fact that spontaneous quitters are more successful than those who get help (*69*) implies that they are either more strong-willed and independent, primed to give up the habit because of other negative factors, or less dependent upon cigarettes. West's description (*145*) of ex-smokers is that they are more likely to be male, older, have smoked less before cessation, started smoking at a later age, have a milieu that is supportive of their stopping, and have fewer indices of neurosis and few psychosomatic symptoms. Lebowitz and Burrows (*77*) discuss the finding that ex-smokers have higher incidence of diagnosed disease and less incidence of symptoms when compared to smokers, suggesting that when it "becomes official" that smoking caused an illness, the smoker will quit more readily than if his symptoms are unattached to etiology or specific pathology.

Another possible effect of cessation may be decreased "chest pain" in those having gastroesophageal reflex, as discussed by Bennett (*10*).

By far the the most common, and clinically the most important, symptom to appear following withdrawal from tobacco is craving for tobacco. The best estimates indicate that 90 percent of all smokers in withdrawal will verbalize their need for cigarettes (*41*). Moreover, among smokers who have been abstinent for 5 to 9 years, one out of five report that they continue to have at least an occasional craving for tobacco (*34*). The importance of craving lies not in its universality or persistence, but in its relation to the clinical goal of modifying smoking behavior. Indeed, the importance of the tobacco withdrawal syndrome in its entirety is based on its provocative role in causing relapse among abstinent smokers.

Dependence

As stated earlier, characterizing tobacco use as a dependence process necessarily raises the issue of tobacco withdrawal. Some authorities believe an abstinence syndrome is crucial to the definition of drug dependence. Indeed, some of the initial reluctance to label tobacco as a

dependence-producing substance rested on doubts concerning the existence of a tobacco withdrawal syndrome. This was the position taken by the Surgeon General in 1964, when first alerting the country to the dangers of tobacco. Since then, there has been an accumulation of studies which suggest that withdrawal from tobacco does produce a variety of signs and symptoms which can be characterized as a *tobacco withdrawal syndrome*. Although the syndrome is variable and is only roughly described and understood, its existence is no longer a matter of great controversy. It is characteristic of withdrawal syndromes that their severity is dose-dependent (*60*). Therefore, it is expected that heavy smokers would report more severe withdrawal symptoms than light smokers.

The inconsistency of the effect of deprivation is reflected in the literature. Studies by Myrsten, et al. (*92*) and Mausner (*83*) report no differences in this regard between light and heavy smokers. In contrast, Burns (*15*) reports that subjects who suffered withdrawal symptoms had smoked an average of 6.9 cigarettes/day more than asymptomatic subjects ($p<.01$). Wynder, et al. (*152*) report that the proportion of abstinent smokers reporting more than one withdrawal symptom increases with baseline consumption.

Another possible confounding factor is that, because smokers can vary their smoking consumption in other ways—depth of inhalation, number of puffs, etc.—cigarette consumption may actually be a very poor measure of dose. Also, differences in nicotine metabolism introduce variability in dose even among those who consume similar amounts of nicotine. Thus, estimating a smoker's dose may require measuring serum levels of nicotine or its metabolites. In the one study which has approached this problem, Zeidenberg, et al. (*154*) found among men a higher and significant correlation between serum cotinine levels before treatment and self-reported "degree of difficulty" in smoking cessation. There is some indication that the severity of the abstinence syndrome is dose-dependent, but much ambiguity remains. Because dose dependency is so characteristic of withdrawal syndromes from other substances, establishing this effect for tobacco would be an important step toward an understanding of tobacco dependency. Further research into the relationship should probably proceed along the lines followed by Zeidenberg, et al., using serum cotinine levels rather than cigarette consumption as the independent variable. Dependent measures should include more refined instruments than Zeidenberg and his coworkers' estimates of "difficulty" and should explore both the number of withdrawal symptoms and their severity.

Two studies have focused upon the diurnal variations in withdrawal symptoms (*79, 87*). Data from a study by Meade and Wald (*87*) show that craving in abstinent smokers and in "ad lib" smoking have the same diurnal pattern; that is, the lowest peak occurs when the subject

wakes up, gradually rising to a peak in the evening, then falling again at bedtime. Thus, there is a consistent function which describes three different stages of the habit and its control (unrestricted smoking, abstinence, and relapse). The meaning of the underlying function has not been determined. Two different types of explanation are plausible. One focuses on diurnal variation in the internal environment of the smoker, suggesting the influence of some metabolic factor with diurnal variation. The other explanation focuses on the diurnal variation in the social environment, e.g., the timing of work, meals, social contact, recreation, and so on, which affects craving for tobacco. Research which accurately measures craving and relates it to environmental stimulus events and circadian variations in the internal environment could help to decide between these explanations. A more comprehensive understanding of how craving varies with stimulus events and with time of day might prove helpful in designing interventions which help prepare smokers to cope with their craving.

Time Course and Duration

While the time course of the abstinence syndrome following abrupt withdrawal from other dependence-producing substances has been systematically studied (*60*), assessment of the course of the tobacco withdrawal syndrome is made difficult by the subtlety and variability of the symptoms (*139*).

The onset of the syndrome appears to be rapid. Changes in mood (*115*) and performance (*93*) are evident. Early effects are not easily distinguishable from the absence of nicotine effects or the effects of simple frustration. Another study reports data suggesting a decrease in symptoms over time (*41*).

After a marked decline in the first week, the tobacco withdrawal syndrome becomes increasingly less yielding. Estimates of the tobacco withdrawal syndrome's duration have been made in retrospective studies which ask ex-smokers to recall how long their discomfort or "difficulty" lasted. However, these studies produce contradictory findings. Burns (*15*) reports a range from 1 to 12 weeks, and Wynder, et al. (*152*) report that most symptoms were gone after 4 weeks. In contrast, Mausner (*83*) reports that, of the ex-smokers who ventured an estimate, fully two-thirds stated that their difficulty had lasted between 1 month and 5 years. In another retrospective study, 21 percent of the sample of ex-smokers reported at least intermittent craving for cigarettes 5 to 9 years after cessation (*34*). Thus, the duration of the tobacco withdrawal syndrome appears to be extremely variable, and no definitive estimate is yet available.

Degree of Deprivation

Even with continued use, reduction in the dose of a dependence-producing substance typically results in the emergence of a withdrawal syndrome (*60*). It has been shown that smokers who changed to low-nicotine cigarettes often report the gamut of acute withdrawal symptoms described above (*32, 114*). Abrupt and total withdrawal from tobacco, however, is associated with a withdrawal syndrome that subsides more quickly and is no worse than that seen in partial abstinence.

Gradual Reduction and Chronic Withdrawal

Despite the usefulness of gradual withdrawal in other dependency disorders, and despite the congruence of this method with sound behavioral principles, there is considerable evidence suggesting that gradual withdrawal from tobacco is associated with treatment failure (*26, 41, 82, 138*). This discrepancy may be explained by the observation that partial abstinence from smoking leads to *more*, rather than less, discomfort in withdrawal. The result is that a partially abstinent smoker is in a chronic state of withdrawal. Typically, this chronic state of withdrawal leads to relapse and a return to baseline rates of smoking (*26*).

Although this explanation is plausible and fits the data available, it must be treated with caution pending further research. Since all of the research relies on smokers who have chosen whether to quit "cold turkey" or by gradual reduction, there is still the possibility that smokers in some way predisposed to experience a protracted withdrawal syndrome disproportionately choose the gradual reduction method. What is needed is experimental research in which smokers are randomly assigned to "cold turkey" or gradual reduction groups and in which the effects on the course of the abstinence syndrome are evaluated.

Another direction for new research might be to determine the threshold for the onset of the abstinence syndrome in gradual reduction. Perhaps there is some rate or degree of reduction which would not precipitate withdrawal, so that a smoker *could* be weaned from tobacco. In addition to a "rate of reduction" parameter, the onset of severe withdrawal may also be controlled by the absolute dose as well. The relationship between degree of tobacco deprivation and the emergence of withdrawal symptoms deserves further study.

Other Factors Possibly Affecting the Abstinence Syndrome

In addition to the factors already cited, the tobacco withdrawal syndrome may be affected by a number of other variables whose influence remains to be determined. One could speculate, for example, about differences between types of smokers in the severity, pattern,

and course of abstinence. A study by Ikard and Tomkins (*56*) suggests that "addictive smokers" experience more severe craving. The smokers in this study were deprived of tobacco only for three hours, however, so that the effects of this typology on the clinical abstinence syndrome are still essentially unknown and deserving of study. Other individual difference variables also deserve study. For example, smoking history, especially such variables as previous attempts to quit and the reason for failure, may affect the withdrawal syndrome. Since the symptoms of withdrawal are relatively ill-defined, the smoker's expectations and set are probably related to his experience of abstinence, as is his motivation to quit (*6*).

Another major factor whose relationship is potentially important, but unexpected, is sex. There is fragmentary evidence suggesting that the abstinence syndrome is more severe in women than in men. Unfortunately, relevant data are too seldom analyzed for this sex difference. For example, Guilford (*41*) reports data separately by sex, but does not submit it to statistical analysis of the sex difference. Yet, of 18 major symptoms reported by her subjects in the first 4 days of abstinence, 15 show some sex difference. Among these 15 symptoms, 13 are more frequently reported by women. The difference is statistically significant (sign test, $N = 15$, $r \leq 2$, $p < .005$). Data reported in a number of other studies line up in the same direction, though the effect fails to reach significance in the individual studies (*104, 131, 152*).

It seems likely, then, that women report more abstinence symptoms than men. The importance of this finding lies in its possible relation to another sex difference in smoking cessation: it is well established that women are more likely to fail in smoking cessation efforts. Guilford (*41*), for example, has presented data suggesting that the relationship between withdrawal symptoms and failure in smoking cessation is stronger for women than for men. Thus, women experience more discomfort in withdrawal and are more affected by it in their attempts to quit smoking. It seems likely that this is at least partly responsible for their lower rates of successful cessation.

Nor are organismic variables the only variables relevant here. The method used to achieve cessation may well have an effect on the subsequent withdrawal syndrome. Environmental factors, such as the smoker's social environment, are potentially powerful determinants of the smoker's experience of withdrawal. These and other events, such as social drinking, may produce conditioned craving and are to be considered high risk situations for relapse (*79*). Thus, in addition to the few factors whose influence on the tobacco withdrawal syndrome is known, there are many other potentially important variables whose effects remain to be determined.

Techniques for Measuring Tobacco Usage

The question of how to measure the use of cigarettes is an important one when evaluating the various methods of cessation and the benefits of cessation versus the risks of continuance, and when determining the validity of the reports of study subjects' compliance. (It may also be important in "quantifying" risk factors for disease in current smokers, such as type of cigarette, inhaling pattern, and so forth.) There are five potential sources of information to determine whether or not a person has smoked: urine, blood, breath, saliva, and verbal.

Urine

In the urine, one can assay for the constituents of the cigarette smoke itself or for excretion products that are associated with the physiological effects. Using the Goldbaun and Womanski method, Prado and associates (*107*) measured nicotine excretion in smokers averaging 20 cigarettes/day and found nicotine in the urine in concentrations varying directly with number of cigarettes and inversely with pH of the urine. When deprived of cigarettes for 12 hours, there was no nicotine found in the urine. Trojnar (*133*) compared the urine quantities of adrenaline, norepinephrine, vanilinomandelic acid (a derivative of epinephrine and norepinephrine via monoamine oxidase and catecholamine-o-methyl transferase), and 5-hydrosyindolacetic acid in nonsmokers and those who had quit for at least 6 months. The nonsmokers' and quitters' levels were indistinguishable until the ex-smokers smoked an average of 14 cigarettes. Urine metabolite levels, with the exception of norepinephrine, rose when measured on the second day, (EPI 2.04 g/day, VMA 1.31 g/day, SHIAA 2.4 g/day). In a second study, Trojnar (*132*) found that all four values were increased in smokers over nonsmokers without any discontinuance.

A potential problem in measuring the physiological metabolites associated with smoking is in false positives. This can occur when a subject may have experienced severe anxiety, with increased catecholamines, but did not smoke. The urine nicotine level would seem to be more specific, but both methods would have to be used every 12 hours or less to be accurate.

Blood

One constituent found in blood is carbon monoxide, combined to form carboxyhemoglobin (COHb). Sillett, et al. (*121*) describe the simplicity of using the I.L. 182 CO-Oximeter and the potential for giving subjects quick feedback on their performance. They also say it is possible to detect when those who switch from cigarettes to cigars continue to inhale. Turner (*134*) points out that the average nonsmoker's blood in London has 1.3 percent COHb and that 2 percent is used as a suggestion that smoking has resumed. As cities vary in CO in the air,

standards would have to be set depending on locale. When Ohlin, et al. (*97*) confronted 32 patients at an antismoking clinic with their elevated COHb levels, 13 immediately changed their report, admitting recidivism. When considering COHb, one must take environmental and occupation sources of CO into account. Although COHb increases proportionally with number of cigarettes (*125*) and varies with nicotine content (*111*), discretion is necessary in using data.

Serum cotinine levels may be a reliable tool in determining cessation, according to Zeidenberg, et al. (*154*). With a half-life of 30 hours, as opposed to nicotine's 30 minutes, and the relative constancy of the cotinine levels in regular smokers, it is possible in this way to evaluate long-range abstinence.

Breath

The determination of mean alveolar CO partial pressure described by Rawbone, et al. (*108*) makes it possible to determine the carboxyhemoglobin levels of the blood with a correlation of $r = .96$. Also, by subtracting expired CO from inspired, it is possible to determine if a smoker is an inhaler. Vogt, et al. (*142*) used expired CO and serum thiocyanate to assess exposure to cigarettes. Smokers had higher levels of both (CO 8 ppm, SCN-100 μmol/l)—three times greater in those smoking more than a pack a day than in nonsmokers. The correlation between smoking and each variable separately was less than the two combined (CO = .476; SCN = .479; both = .571). The researchers were 99 percent accurate in separating "typical" smoking habits from nonsmokers' habits and hypothesized the possibility of grading intermediate levels for exposure to smoke. No mention was made of environmental or occupational sources of CO or CN.

Saliva

The presence of nicotine in saliva can be determined by gas chromatography and an alkali flame ionization detector (i.e., nitrogen detector) (*31*), but it is difficult to distinguish a pattern of smoking. Nonsmokers separated from smokers can be distinguished from nonsmokers who smoke passively. While this is a sensitive method of measurement, the presence of nicotine in saliva does not prove direct use of tobacco. Using this method, it may be possible to determine a maximal level attainable by passive smoking and use that value as a cut-off in determining probable usage.

Tenovuo and Maekinen (*130*) measured thiocyanate and ionizable iodine in saliva with the following results:

	Thiocyanate (mg/liter)	
	Males	Females
Smokers	210±75	124±46

Nonsmokers	91±44	62±32

	Ionizable Iodine	
	Males	Females
Smokers	7.2±.9	10.1±3.6
Nonsmokers	13.4±9.7	13.9±8.0

Although controls using the same subjects, both smoking and abstaining, were not employed, this technique can adequately separate the values of smokers' and nonsmokers' thiocyanate, especially for males. It should be noted, however, that the overlap between smokers and nonsmokers is considerable and that Vogt found no correlation between the tar content of cigarettes and the thiocyanate levels in saliva.

Verbal

Although there are several biological assays measuring use of cigarettes, McMahan, et al. (*86*) propose using the verbal report of the subject, confirmed by an appropriate associate of the subject. They point out that the correlation between reports of the subject and the associate about the subject's smoking behavior is $r = .86$. While the correlation indicating that the subject and associate agree is encouraging, that may be all this study says. A smoker who does not want the researcher to know his smoking habit accurately will probably either not allow the associate to see him in his true habit or will encourage the associate to "interpret" his smoking pattern along the lines he wishes to portray. Other methods may be used, such as a lie detector, but unfortunately they are beatable.

The only "fool-proof" method of determining use is to observe the subject at all times. Even here the degree of inhalation cannot be accurately determined. Since this approach is highly impractical, biological tests must be employed, and understanding of the potential source of inaccuracy must be considered before drawing firm conclusions. Based on the above descriptions, it would seem that the most practical method would be measurement of nicotine, cotinine, and thiocyanate in the urine. If none of these is found in the urine, the conclusion is that the subject has not smoked (or has borrowed urine). If some nicotine is found in the urine, could it have been from passive smoking? One should note, too, that quantitative analysis of nicotine in body fluids will take on increasing significance, since tar and nicotine levels are being decreased in cigarettes, and researchers will need to know not only whether a subject smoked, but how much.

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