Section 7. BEHAVIORAL ASPECTS

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Summary

References

This section outlines the future directions that research on lower "tar" and nicotine cigarettes should take. These are: (1) to perform additional laboratory studies under controlled experimental conditions; (2) to conduct additional research on compensatory smoking; and (3) to investigate both the biological and psychological factors involved in smoking.

Research Priorities

Controlled Studies To Determine the Role of Nicotine as a Primary Reinforcer in Cigarette Smoking

Many important questions on the pharmacological importance of nicotine in maintaining cigarette smoking remain unanswered, despite a large number of studies on the topic *(1, 2, 19, 25, 36, 44, 46, 49, 65, 69, 73).*

Nicotine is probably the primary source of the pharmacodynamic appeal of tobacco, but not enough is known about its exact role in smoking to determine whether it is the only source. (For reviews on nicotine and smoking, see *18, 21, 31, 57, 61.)*

Tobacco without nicotine appears not to be sufficiently reinforcing to support sustained use *(18).* There has never been an appropriately designed study with a large number of subjects randomly assigned to smoke flavor-balanced cigarettes of varying nicotine content over a substantial (months) time period. The behavioral aspects of cigarette smoking are of paramount importance in the evaluation of leas hazardous cigarettes. Behavior is the interface between cigarette smoking, its pharmacological and physiological effects, and the generation of disease. Compensation for nominally reduced machine-measured "tar" and nicotine yields of cigarettes by increased depth and volume of inhalation as well as proportion of the burning cigarette consumed has been demonstrated. Such a study would be necessary to conclusively support this hypothesis of cigarette habituation.

Instead, we can only look at the distribution of smoking by nicotine yield and the experimental literature. In 1979, the percentage of current regular smokers in the United States who smoked cigarettes low in nicotine content (less than 0.5 mg nicotine and less than 5 mg "tar") was very small, about 4 percent. Research studies using tobacco cigarettes virtually free of nicotine show these to be rated as aversive by smokers *(36, 64).* At the same time, it has been difficult to demonstrate that smokers will use nicotine in a nontobacco medium. In one study, lettuce leaf cigarettes injected with nicotine were smoked for 1-week periods at intake levels only approximately 50 percent the rate of the subject's own brand, and with protest of much reduced satisfaction *(13).* Considered a more direct route of administration, injections of nicotine became a satisfying replacement for cigarettes

after repeated trials, but this early study was not conducted in a "blind" fashion *(38).*

More recent studies of intravenously administered nicotine have contained subjective reports of perceived pleasure *(39),* but also have included reports of an inability to suppress subsequent smoking to a major extent *(39, 46, 49).* Although the results were perceived as only mildly pleasurable, nicotine administered in oral tablet form *(35)* or embedded in chewing gum *(44, 64)* has decreased various measures of smoking in individuals not trying to quit.

The major problem with giving nicotine in other than inhaled form is that it lacks some of the biological as well as many of the behavioral similarities to smoking. The nicotine bolus, when inhaled, reaches the central nervous system in less than 8 seconds *(58).*

More information is needed to understand the pharmacological, psychological, and situational cofactors that may contribute to the reinforcing effects of nicotine. By analyzing the mechanisms whereby nicotine reinforces smoking behavior, it may be possible to design more efficacious treatments for cigarette dependence or to devise techniques for maximizing the rewards of smoking while minimizing the risks to health.

Animal Models of Nicotine Use

Animal models have several advantages over human models in studying the effects of nicotine. In the animal laboratory, environmental variables can be controlled to a much greater extent than they can in the human laboratory. History of exposure to the drug can be manipulated in a true experimental fashion. One of the greatest limitations of much epidemiological and behavioral research on human smoking behavior is that the subjects are self-selected. Consequently, the research is inherently correlational rather than experimental. Correlational research can describe associations between variables, but it is often confounded by unmeasured variables *(30).*

Animal models have been used to study the dependence liability and toxicity of many drugs *(17, 75).* The techniques used in analyzing responses to other drugs should be developed further and applied to the study of nicotine-and perhaps other substances in tobacco.

Methods of administration can have a large effect on the pharmacokinetics of nicotine. Oral, intravenous, and inhalation modes of administration should be employed, but since smokers receive nicotine from inhaled smoke, the inhalation route is particularly important. Unfortunately, animals do not inhale nebulized nicotine or cigarette smoke in ways that are comparable to human inhalation patterns *(53).* Until reliable inhalation methods for animals are perfected, intravenous administration will have to be used in much of this research.

The Self-Administration of Nicotine by Animals

Since people take nicotine on their own, an ideal animal model would be one in which animals take nicotine on their own. Attempts to get animals to administer nicotine to themselves have not been uniformly successful *(17, 21).* Maintained self-administration has been found in the monkey and the rat in some studies *(6, 22, 47, 50),* but not in others (82). Recent work has shown that under some schedules of reinforcement, monkeys will self-administer injections of nicotine *(12).* In order to discover precisely what variables are critical to the reinforcing properties of nicotine, further studies are needed.

In addition to studying the parameters of self-administration, toxicity should also be measured. For example, it is important to look at the variables of physical dependence, food and water intake, and morbidity, as well as necropsy findings.

The Study of Tolerance and Physical Dependence

Both tolerance and physical dependence can develop to nicotine or other ingredients in tobacco *(33, 48, 71, 78).* Animal models have been used successfully in research on opioids and alcohol *(70)* and could prove effective in future research on nicotine and smoking.

Appropriate animal models would facilitate the study of the pharmacokinetics of nicotine and would help in the evaluation of pharmacological treatments for dependence. Since tolerance and physical dependence can influence the reinforcing properties of drugs of abuse, animal studies should investigate the extent to which withdrawal phenomena may contribute to the reinforcing properties of cigarette smoke. Methods developed for evaluation of opioid drugs could be adopted for these purposes.

Nicotine Research With Humans

The scientific issues in human and animal research are similar, although not all studies conducted on animals are practically and ethically suitable for research on humans. A great amount of preliminary data already exists on the role of nicotine in human smoking behavior (see the reviews cited above), but the influence of tolerance and dependence on nicotine on the initiation, maintenance, and cessation of smoking behavior are still not resolved *(27, 46, 59, 61, 68).* Clearly, both biological and psychosocial factors influence human cigarette intake *(41),* and it is in the human model of cigarette smoking that the interplay of these factors can best be studied. There is no known analog in animal behavior for future orientation and cognitive factors, such as worrying about the risks of cancer or about weight gain upon giving up smoking.

Progress to date in laboratory studies of smoking dependence has been slowed by the lack of standardized test materials, such as

cigarettes made to research specifications, and of standardized, easily accessible laboratory analyses, such as for plasma levels of nicotine.

Compensatory Behavior in Smoking

If, in the course of a standard assay for the "tar" and nicotine yields of a cigarette *(54)*, a smoking-machine derives relatively small amounts of "tar" and nicotine, the cigarette can be called lower "tar" and nicotine. Unfortunately the smoking-machine model is limited in accurately reproducing human smoking behavior. The machines take a 2 second, 35 cc puff each minute until a predetermined butt length is reached. Smokers, however, are able to take larger, more frequent, and higher velocity puffs than the machines do. It appears that such compensatory adjustments often turn nominally lower "tar" and nicotine cigarettes into higher "tar" and nicotine cigarettes *(1, 4, 9, 25, 36, 46, 60, 62)*. Even if the compensations made in smoking a single cigarette are small or nonexistent, smokers can increase their intake of "tar" and nicotine by smoking more cigarettes *(66)*.

Cigarettes of less than about 6 mg "tar" and 0.5 mg nicotine are also subject to the influences of compensatory smoking. Most of these cigarettes achieve their lower yields as a result of ventilation holes placed in the filters, which cause each puff of smoke to be diluted with air. These air-diluted puffs deliver relatively small amounts of "tar," nicotine, and carbon monoxide to the smoking-machines *(29)*. Some smokers have learned to block the ventilation holes with their lips or fingers-or sometimes with tape-and thereby, often unwittingly, defeat the purpose of the holes. If the ventilation holes are blocked, yields of nicotine, "tar," and carbon monoxide can increase by about two, three, and four times, respectively *(42)*. In 1979, ventilated-filter cigarettes accounted for about 25 percent of total cigarette sales *(29)*.

Many studies have used estimates of nicotine and smoke intake baaed on direct observations *(44)*, measurements of smoking topography by means of special cigarette holders *(24, 36)*, or analyses of residual nicotine in cigarette filters *(1, 9, 55)*. Only a few studies have measured the levels of nicotine in plasma as a function of the nominal smoking-machine yields *(1, 63)*, but research indicates that some smokers do compensate for reduced yields of nicotine.

By smoking more to compensate for lower nicotine intake, lower "tar" and nicotine cigarette smokers can inadvertently increase their exposure to "tar" and carbon monoxide beyond what might be expected from a less intensively smoked higher "tar" and nicotine cigarette *(57, 67)*. Because less hazardous cigarettes may require the delivery of moderate levels of nicotine while delivering lower levels of "tar" and carbon monoxide, Russell *(57)* has proposed that lower "tar" to nicotine ratios should be used to indicate less hazardous cigarettes. These ratios may direct smokers to potentially less hazardous cigarettes, but the way in which a cigarette is smoked can affect the ratio

of "tar" and nicotine entering the body *(5, 45)*. It is not yet clear how accurately machine-determined ratios can predict human intake of "tar" and nicotine.

Compensatory smoking is central to the question of the public health benefits of lower "tar" and nicotine cigarettes. The frequency and extent of compensatory smoking should be measured in detail in order to determine whether smokers who switch to lower "tar" and nicotine cigarettes actually inhale fewer harmful compounds. Two types of studies of brand-switching behavior are needed: voluntary (naturalistic) switching and controlled (experimental) switching. These studies should be carried out over several months and include topographical, pharmacological, biochemical, and physiological measures in order to characterize the degree and nature of compensation. Research should address the question of the acceptability of lower "tar" and nicotine cigarettes and should measure smoker satisfaction with them. A low-risk cigarette serves its purpose only if people will smoke it in a way that truly yields lower "tar" and nicotine.

The issues of self-regulation of smoke intake and acceptability have been discussed by Russell *(60)*.

Voluntary Switching

Little is currently known about smokers who have adopted lower "tar" and nicotine cigarettes, but detailed prospective studies of voluntary switching would reveal how exposures to nicotine and carbon monoxide change as smokers switch to those cigarettes. Data do exist on plasma nicotine levels *(62)* and COHb levels *(79, 80)* from lower "tar" and nicotine cigarettes, but these studies are cross sectional. They suggest that lower "tar" and nicotine cigarettes may not be particularly "low yield" to those who have chosen to smoke them.

Jaffe et al. *(32)* used monetary incentives and health messages to encourage switching to cigarettes with lower "tar" and nicotine delivery in a series of studies on female smokers. Cross-sectional data on smokers who were already smoking lower "tar" and nicotine brands with substantially reduced nominal carbon monoxide delivery revealed that these smokers had alveolar carbon monoxide levels as high as smokers of higher "tar" and nicotine brands, as well as comparable levels of saliva thiocyanate. Preliminary results from the prospective study of voluntary switching, still in progress, show significant reductions in nominal daily nicotine intake and only a few instances of a significant rise in carbon monoxide upon switching.

Epidemiological research on smoking cannot be done rapidly; it will take several years to evaluate possible reductions in the health risks of lower "tar" and nicotine cigarettes, Behavioral studies on voluntary switching, however, can provide estimates of health risks. If further research indicates that exposures to toxic products do not decrease in those who change to lower "tar" and nicotine cigarettes, then a re-

examination of the advisability of encouraging people to switch to milder cigarettes should be undertaken. (See Russell *(60)* for a brief discussion of the possible role of self-selection biases in the epidemiological finding that filter-tipped cigarettes are less hazardous *(3, 81).* See Harris *(23)* for a summary discussion of behavioral and economic factors affecting the promotion of lower "tar" and nicotine cigarettes.)

Controlled Switching

Very few studies on controlled switching have employed measures of plasma nicotine *(1, 28, 60).* No large-scale studies have been conducted that make use of plasma nicotine, carbon monoxide, and physiological measures of smoke exposure.

The relationship between smoker satisfaction and compensatory smoking appears to be complex. One forced switching study *(74)* has shown that, even though the compensation was incomplete and did not change for the few days of the study, satisfaction did improve during the course of the experiment. We do not know if satisfaction with lower "tar" and nicotine cigarettes increases with duration of their use, if it decreases with time if compensation occurs initially, or if nicotine yield alone determines cigarette acceptability.

Additional Comments

As noted earlier, progress in compensatory smoking research has been hindered by the lack of research cigarettes varying systematically in nicotine, "tar," and carbon monoxide, and by the shortage of laboratory facilities in which to do needed analyses.

One byproduct of the proposed research on switching to lower "tar" and nicotine cigarettes might be the development of practical diagnostic techniques. Smokers and physicians have not determined whether lower "tar" and nicotine cigarettes have produced "low-yield" smoking, but simple measures such as expired air carbon monoxide *(11, 26)* might help supply needed information concerning smoke exposure.

Natural History of Smoking Along Both Biological and Psychosocial Dimensions

Since almost nothing is known about the role of lower "tar" and nicotine cigarettes at crucial transition points in a smoker's history, this issue cannot be considered in detail *(7, 20, 40, 52, 56).* One key unanswered question is whether lower "tar" and nicotine cigarettes tend to facilitate taking up the smoking habit. Presumably, initiation of smoking is easier for those who first try lower "tar" and nicotine cigarettes than for those who first try regular cigarettes. Thus, lower "tar" and nicotine cigarettes can reduce aversive physical responses to early smoking episodes that might otherwise deter taking up the habit *(43, 56).*

Teenagers generally prefer moderately high-yield cigarettes *(77),* but 2.5 percent of the boys and 12.3 percent of the girls who smoke use lower "tar" and nicotine brands (here defined as <= 10 mg "tar"). Research has not addressed the question of what percentage of these smokers may have been helped either in their initiation to smoking or in their shift from casual to habitual smoking by the use of lower "tar" and nicotine cigarettes. The incidence of smoking among teenage girls has increased during the past 10 years *(76, 77).* Silverstein et al. *(72)* present data supporting the hypothesis that the increasing availability of lower "tar" and nicotine cigarettes has encouraged this increase in smoking. Analysis of a survey of high school students suggests that girls experience greater social pressure to smoke than do boys, and that they also face greater physiological pressure not to smoke because of their higher sensitivity to nicotine. Girls appear to resolve these pressures by becoming lighter smokers than boys and by switching to lower "tar" and nicotine cigarettes. Perhaps if lower "tar" and nicotine cigarettes were less available, some girls would choose not to smoke rather than to experience unpleasant nicotine reactions.

Most research on the initiation of smoking and casual smoking has been psychosocial. No doubt there are practical, if not ethical, constraints on studying biological influences on smoking among teenagers. Whatever the reason, very little is known, for example, about the role of nicotine in early smoking experiences. No one knows how much exposure (days, months, years) to smoking is needed before withdrawal symptoms appear. More balance is needed in research on teenage smoking. Whenever possible, biological factors-both physiological and pharmacological-should be studied along with psychosocial factors *(27, 41).*

There has been little research on the effects of lower "tar" and nicotine cigarettes on maintenance or cessation of smoking. There are studies on the effects of using decreasing amounts of "tar" and nicotine as a cessation or reduction aid *(10),* but these studies do not include biochemical or physiological measures of change in smoke exposure. It seems plausible that the alternative of a supposedly less-hazardous cigarette might make some smokers less likely to try to abstain completely. By the same token, the example of a satisfied, though perhaps fully compensating, smoker of lower "tar" and nicotine cigarettes might make a former smoker more likely to relapse. The former smoker might view the lower "tar" and nicotine cigarettes as both acceptable and safe *(14, 15).* Answers to these questions can have immediate implications for smoking treatment. Research in this area should include such crucial variables as gender *(72).* Both experimental and epidemiological data are needed in these studies. Perhaps large-scale smoking surveys can be expanded to include more questions that would help characterize the natural histories of smokers.

Clinical Testing Facilities and Standardized Research Cigarettes

There has been an active research effort in this country on the behavioral aspects of smoking. To further its productivity and to refine the scientific questions that this research can address, especially with regard to lower "tar" and nicotine cigarettes, the facilities and research cigarettes described here are needed.

Clinical Testing Facilities

These facilities should be able to provide biochemical and pharmacological analyses of assays for plasma nicotine, cotinine, carboxyhemoglobin, and salivary thiocyanate. (Jarvik *(34)* reviews the use of these assays.) Each of these assays can be used to measure a smoker's exposure to some of the toxic and/or reinforcing ingredients in tobacco smoke. Plasma assays for nicotine *(8)* are available in a few laboratories; these assays can require special facilities to avoid problems of contamination. For example, a laboratory that is used part of the time by a worker who smokes may be unacceptable for the evaluation of plasma nicotine levels. Few behavioral researchers have access to or sufficient control over the needed laboratory facilities. Laboratories of this nature would be a great boon to behavioral research and would help to standardize assays in this area.

Research Cigarettes

A supply of clinically acceptable cigarettes that vary in nicotine, "tar," and carbon monoxide yield should be made available to behavioral researchers. Although some standardized cigarettes have been available for years from the Tobacco and Health Research Institute of the University of Kentucky, these cigarettes have no filters, and their lack of palatability and acceptability almost completely precludes their use in behavioral research. Cigarette technology has several ways of altering "tar," nicotine, and carbon monoxide yields. Ideally, different strategies would be employed to produce cigarettes with identical machine-smoked yields. Consider two examples. A fast-burning, strong-tobacco cigarette might have the same yields as a slow-burning, mild-tobacco cigarette, but it is not clear how human smoking behavior might change as a function of these modes of yield reduction. A cigarette low in carbon monoxide could be made with either vented cigarette paper or a vented filter. The vented filter can be closed by smokers accidentally or intentionally, thereby increasing the actual yield to the smoker *(42)*, but the effect of porous cigarette papers cannot readily be circumvented by the smoker.

Variations in "tar" to nicotine ratios should be of special concern *(57)*. It is important to determine the lowest ratios that still produce a satisfying cigarette. Obviously, identical "tar" and nicotine ratios can

occur in cigarettes that have very different standard nicotine yields. Research could show if there is an optimum combination of standard yield and ratio that leads to maximum satisfaction and minimal exposure to toxic products. Cigarettes that vary systematically in "tar" to nicotine ratios are needed for this research.

Machine-Smoked Yields of Lower "Tar" and Nicotine Cigarettes

The standard smoking-machine assay of "tar" and nicotine yields provides inadequate information to the tobacco consumer as well as to the researcher *(16, 45, 74).* The published yields do not indicate how many puffs were taken on a particular brand *(45);* assays at the Oak Ridge National Laboratory *(37)* reveal that from 6.9 to 11.5 puffs are taken on different brands of king-size filter cigarettes during standard assays.

The current smoking-machine standards are meant to represent an average smoker, but it is probable that the standard puff volume (35 cc) is too small *(5, 51)* and that the puff interval (one puff per minute) is too long *(4, 74).* Since compensatory smoking occurs with lower "tar" and nicotine cigarettes, larger and more frequent puffs tend to be taken. Smokers sometimes interfere with ventilation holes on lower "tar" and nicotine cigarettes *(45);* smoking-machines do not.

In addition to the standard assays, there should be maximum-yield assays of "tar," nicotine, and carbon monoxide. These assays would be based on puffing parameters of volume, rate, and duration for the 95th--or even the 75th--percentile of heavy smokers smoking lower "tar" and nicotine ventilated cigarettes up to the tip overwrap. These parameters would be used in smoking-machines, with these same ventilated brands, to derive yields with ventilation holes in both blocked and unblocked conditions. This procedure would produce much higher yields than does the standard assay, and these values would better represent the possible maximum risks of the lower "tar" and nicotine cigarettes to smokers who engage in compensatory smoking. Without access to information about how much the standard yields can change with intensive smoking, there can be only a limited understanding of possible reductions in actual smoking exposure. Using research in the British-American Tobacco Company Laboratories in the United Kingdom, Green *(16)* has argued that intensive smoking can make middle "tar" cigarettes (11 to 16 mg) deliver as much as high "tar" cigarettes (31 to 35 mg). Green could not demonstrate that low "tar" cigarettes (0.4 to 9 mg) can be made to deliver high "tar" levels, but this study did not consider the effect of blocking the ventilation holes on these cigarettes.

Toxicology of Nicotine

A probable outcome of behavioral research will be that nicotine is the primary pharmacological reinforcer for cigarette smoking. If this

prediction is correct, a lower "tar" and nicotine cigarette that will be used by smokers and that will minimize the exposure to other toxic components of smoke may require substantial yields of nicotine *(57, 62)*. Consideration of the toxicity of nicotine, then, may become crucial in determining whether the benefits of lower "tar" and nicotine cigarette smoking outweigh the costs.

Summary

1. Nicotine appears to be the primary pharmacological reinforcer in tobacco, but other pharmacological and psychosocial factors may also contribute a reinforcing effect.
2. It appears that some smokers make compensatory adjustments in their smoking behavior with cigarettes of different yields that might increase the amounts of harmful substances entering the body. The frequency and amount of spontaneous compensatory changes in smoking style with different cigarettes require further investigation.
3. Additional information is needed on the role of lower "tar" and nicotine cigarettes in the initiation, maintenance, and cessation of smoking.
4. Rigorous comparative behavioral studies involving animals are needed to provide comprehensive, experimentally valid results on behavioral aspects of smoking.
5. Laboratory techniques developed for study of opioids and alcohol should be adapted for studies of tolerance and dependence on nicotine.
6. Improved laboratory facilities are necessary for more tightly controlled behavioral research. A particular need exists for clinically acceptable cigarettes with standardized ingredients.
7. Smoking-machine measurements that more closely simulate the practices of human smokers must be developed.

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