

Agricultural Practice

The chemical composition of tobacco leaf is also affected by agricultural practice and by curing methods (161, 163). High levels of nitrogen fertilizer increase nicotine and nitrate levels of the leaf. Growing plants more closely together reduces the nicotine content of the leaf. Flue-cured tobaccos are harvested, leaf by leaf, as each is ripe, but the entire plant of burley tobacco is harvested at once. Changes associated with leaf maturity depend on the harvesting practice. Enzymatic degradation of leaf constituents is halted by heat during flue curing. In contrast, burley, Maryland, and oriental tobaccos are not heated to this extent, so that more extensive enzymatic changes occur. As a consequence, there is a markedly lower sugar content in burley tobacco along with a markedly higher content of pigment polymers. Homogenized leaf curing (HLC), if commercially developed, could permit better control over these chemical changes. Furthermore, specific leaf constituents such as soluble proteins may be removed during homogenized leaf processing. Cigarettes made with HLC tobacco yielded smoke containing significantly less dimethylnitrosamine and condensate having significantly less sebaceous gland suppression activity (165, 169).

Reconstituted Sheet and Modified Tobaccos

The composition of cigarette smoke is also affected by the use of reconstituted tobacco sheet and modified tobaccos (62, 63, 64, 65). Reconstituted sheet can contain substantial amounts of the tobacco "stem," which has a different composition from that of the leaf lamina. The stem is noteworthy for having a low nicotine content. In addition, the physical nature of reconstituted sheet can be controlled to change its burning characteristics and hence the composition of the smoke.

In recent years, some cigarette tobacco has been "expanded" or "puffed." Using this material, less tobacco is required to fill the cigarette. The manner in which the tobacco is shredded also affects the burning rate and therefore the composition of the smoke (47). Cellulose-based substitutes have been used as a replacement for tobacco (17, 35). These materials cause substantial differences in the total yield and chemical composition of the smoke.

Additives

Humectants and flavoring agents have long been used as additives in cigarette manufacture. The advent of reconstituted tobacco sheet (RTS) technology expanded the possibilities for the addition of substances to the sheet during the processing of tobacco for the manufacture of cigarettes (174, 188). It is possible to add substances to the tobacco slurry or suspension for extraction of specific constituents, for dilution of the sheet, for burn rate acceleration or retardation, for

ash cohesion, and for enhancement of flavor (smoke aroma and taste) (65, 151). Additionally, one process for curing tobacco leaf calls for the addition of exogenous enzymes to tobacco (169), and as noted above, artificial tobacco substitutes are also available. In recent years, cigarette manufacturers' advertisements have focused on the flavor of new lower "tar" and nicotine cigarettes, enhanced presumably by the addition of tobacco constituents or by the addition of new flavoring materials, such as natural or synthetic chemicals. The identities and amounts of the additives actually used in the manufacture of U.S. cigarettes are not known. Systematic information has not been published or made available on the influence of these additives on the composition or biological activity of cigarette smoke.

Variations in Human Smoking Behavior

It does not appear possible to fully monitor smoking behavior in humans without the subjects' knowledge. Butt lengths can be measured in a variety of settings, and puff frequency can be observed without distorting smoking behavior. Measurement of puff volume and duration and of intensity of inhalation, however, requires instrumentation that may lead to alteration of usual smoking behavior. Nevertheless, despite these limitations in objectivity, recent studies provide better data than those available in the past.

Smoking measurements reported from England, Germany, and Canada differ from those used for smoking-machines in the United States (139, 141, 150). If the average American smoker, as well, is taking larger puffs with a greater frequency than is the machine, the absolute yields of smoke constituents are under-reported in the United States. This is not to say that the relative yield of "tar" between cigarettes is compromised; however, if smokers puff different types of cigarettes in different ways, the relative yields may be grossly distorted. For example, some smokers block the perforations in the mouthpiece of ventilated cigarettes (102). These smokers receive substantially more "tar," nicotine, and gas phase constituents than would be predicted from machine-smoked cigarette yields. Because this action would affect the yield only of ventilated filter cigarettes, the relative ranking of cigarettes by yields would be affected. Similarly, smokers' behavioral compensation for low nicotine delivery can affect the relative yields of filter-tipped cigarettes (80, 142).

Research Needs

Many gaps in our assessment of the pharmacological properties of cigarette smoke can be filled by a coordinated, well-directed research program. In comparison with the economic and medical costs of cigarette smoking, the size of the required program is modest. Resources sufficient for implementation of a meaningful program are

available. For example, except for assays of "tar," nicotine, and carbon monoxide yield, new types of cigarettes are not being monitored regularly for the delivery of potentially harmful smoke constituents. Scientists currently conducting sophisticated assays of cigarette delivery of various smoke constituents could serve as resource personnel in the design of an appropriate approach to assays of new cigarettes for suspected toxic agents. Other scientists are investigating short-term end points indicative of long-term risk from many diseases. These laboratories could assist in modifying these procedures specifically for cigarette smoke and its constituents.

Surveillance of New Cigarettes

The chief research need for the study of reduced "tar" and nicotine cigarettes is the routine and frequent surveillance of current and new cigarettes for specific chemical constituents and biological activity. The chemical constituents should include nicotine, benzo[a]pyrene, phenols, catechols, nitrosamines, carbon monoxide, nitrogen oxides, volatile aldehydes, and radionuclides. The biological assays should include sebaceous gland suppression assays, mutagenesis assays, studies of the effects of smoke on airway and ciliary function and on the increase of urinary metabolites related to the activity of elastase, and such other biological assays as may appear predictive of human disease in the future.

Inherent in this recommendation is the use of quantitative short-term end points for various conditions associated with human disease. We do not have proven animal models for quantitative evaluation of risks of chronic obstructive pulmonary disease, sudden death due to cardiovascular disease, or complications of pregnancy and infancy. Emphasis should be given to developing short- and long-term bioassays aimed particularly at these diseases.

Determination of Parameters of Human Cigarette Smoking

Smokers may smoke different types of cigarettes differently with respect to puff volume, duration, and frequency, inhalation profiles, and the manner in which the cigarette is held by the fingers and in the mouth. To conduct meaningful assays of cigarette yields and of the biological activity of cigarette smoke, it is important to know how smokers consume each type of commercial cigarette. Only when this information is available can smoking-machines be designed to yield the most accurate estimate of human dose. We must know both the average and the range of variation in smoking pattern.

The available studies compare smokers' behavior with commercial cigarettes found to deliver different amounts of "tar" or nicotine. Other changes that occur in the product are often unknown. A second type of study should use prototype cigarettes specifically designed to deliver a wide range of concentrations of a desired constituent; for

example, with high or low nicotine to "tar" ratios. Such a study would define the behavior of smokers of new types of cigarettes before or as they are marketed. These studies, however, would require a particular resource that is not accessible to most investigators. There are a large number of experimental cigarettes differing widely in several respects (62, 63, 64, 65). Unfortunately, they were developed without concern for smoker acceptability and cannot be used to evaluate human response to design changes. A coordinated program should be established to develop a series of clinically acceptable experimental cigarettes that resemble a "reference standard" as closely as possible, differing only in one or two well-defined characteristics. These should then be made available to appropriate investigators for the study of human smoking behavior.

Evaluation of Health Effects of Nicotine

Nicotine has pharmacological significance for man and animals (92). The alkaloid is suspected of playing a role in sudden death due to cardiovascular disease, to the complications of pregnancy and infancy, and possibly to chronic obstructive pulmonary disease. Nicotine in cigarettes leads to the formation of tobacco-specific nitrosamines in the smoke. These are potent carcinogens. Nicotine itself is a significant cocarcinogen in mouse skin carcinogenesis assays of smoke condensate.

It is important to determine whether nicotine acts as a cocarcinogen under the conditions of dosage achieved by cigarette smokers and whether the levels of nicotine-derived nitrosamines play a role in human malignant disease. Resources for such study are available and should be employed in a comprehensive evaluation of the potential carcinogenic effects of new types of cigarettes.

Nicotine should be tested alone, and in the presence of other noxious agents such as carbon monoxide, in animal systems designed to serve as models for nonmalignant diseases associated with cigarette smoke.

Experimental cigarettes with a range of nicotine content have been produced for studies of carcinogenesis. Many of these cigarettes are still available. Those experimental cigarettes that might be needed for pharmacological studies of nicotine should be identified and distributed to appropriate laboratories as the need develops.

The Effects of Smoking-Machine Parameters on Relative and Absolute Yields of Smoke Components From Various Types of Cigarettes

Smoking-machine assays of cigarettes fulfill two needs. The FTC ratings of "tar" and nicotine yields measure an implied risk to the smoker. Smoking-machine data guide experimenters in elucidating the mechanisms of induction of smoking-related disease. Absolute levels of smoke constituents may be very important for experiments, so the experimenter must have reliable information about the comparability

of machine and human smoking. The use of machine data to monitor risk has somewhat different requirements. If the *relative* yields of different cigarettes are not greatly affected by smoking conditions, present smoking-machine standards will be adequate to indicate relative risk of new cigarettes. We know, however, that the relative yield of many constituents is affected by butt length, puff frequency, and degree of ventilation. We need to determine how the variations in these smoking parameters affect relative yields of the several substances in smoke that are of toxicological interest.

Influence of Raw Product Modification on the Pharmacology of Cigarette Smoke

The composition of smoke is determined by the physical and chemical properties of leaf tobacco. Modification of the raw product therefore changes the pharmacology of cigarette smoke. The diversity of available tobacco germplasm along with known genetic techniques permits reduction of hazards in cigarettes through plant breeding and selection. Cultural and curing practices are constantly changing in response to market demands and the needs of farmers. Pesticides currently registered for use on tobacco have been tested as contributors to the carcinogenic activity of cigarette smoke condensates. When used as directed, these materials caused no significant change in biological activity (65, 166). However, the pesticides used in tobacco farming change from time to time in response to the occurrence of new plant pests; for example, the recent spread of blue mold in tobacco-growing regions has led to the use of a new pesticide. It is not known whether the use of such materials may result in changes in the hazards of cigarette smoke.

Present tobacco curing processes may vary somewhat from farm to farm. Furthermore, marked differences in agricultural practices such as close spacing of tobacco plants, bulk curing, and homogenized leaf curing might be introduced in the future. We need to determine the consequences of changes (genetic, cultural, and curing methodologies) on both the chemical composition and the biological effect of cigarette smoke.

Physical and Chemical Properties of Smoke From Cigarettes Delivering Less Than 10 mg of "Tar"

In the past few years, cigarettes delivering less than 10 mg of "tar" by FTC test have been placed on the market. These cigarettes apparently employ efficient filters together with various degrees of smoke dilution. The extreme reduction of "tar" and nicotine delivery by these cigarettes suggests significant differences in combustion processes. Substantial differences in the chemical nature of both mainstream and sidestream smoke might result from such changes.

Some or all of the new lower "tar" and nicotine cigarettes are manufactured by processes that involve the use of chemicals or flavor additives to improve consumer acceptability. The nature of these additives, and their combustion products, that are currently used in marketed cigarettes is not available to the public or to the Government. Likewise, there are no published data on the biologic effects of these additives or their combustion products.

Very low yield cigarettes may add to present concerns with respect to sidestream smoke (5, 157, 184). While these cigarettes may deliver such low levels of "tar," nicotine, and gas phase constituents that smokers cannot compensate completely, the delivery of sidestream smoke may not be reduced. Indeed, the sidestream smoke might contain more of some substances (e.g., pyrolytic products of flavor additives) than does the sidestream smoke of higher yield cigarettes. For very low yield cigarettes, the risk of the sidestream smoke may equal that of the mainstream smoke. The chemical and physical nature of sidestream smoke should be determined on new cigarettes.

Development and Validation of Analytical Methods

Methods for determining "tar" and nicotine yield were developed before very low yield cigarettes were an important segment of the market. It is questionable whether existing procedures can measure accurately the "tar" delivery of the cigarettes yielding 0.1 mg of "tar." Other techniques giving acceptable results must be developed. Procedures for determining "tar" yields of low magnitude through measurement of fluorescence have been recommended (159). These methods must be validated by determining intra- and inter-laboratory reproducibility. Furthermore, fluorescence measurements may be compromised by additives that interfere with fluorescence, either directly or through the behavior of their pyrolytic products. Fluorescence measurements may not be satisfactory for use with new commercial cigarettes.

Analytical procedures must also be validated for a number of chemical constituents in smoke such as aldehydes, nitrogen oxides, phenols and catechols, aromatic hydrocarbons, and nitrosamines. Several laboratories are conducting such assays with favorable results. However, coordinated comparisons among laboratories to measure the degree of intra- and inter-laboratory variability have not been reported.

Other Research Needs

A number of other research needs of lesser priority should be addressed:

1. It is necessary to study the interaction of smoking with occupational and environmental exposure to other noxious materials. The incidence of lung cancer is greatly increased in asbestos workers or uranium miners who smoke cigarettes (3, 70, 117). The

risk of using contraceptive hormones is also greater in cigarette smokers (132, 174). Laboratory models of cocarcinogenesis should be used to measure the potential effect of combined smoking and exposure to other environmental toxins. Animal models should be developed to investigate the possible synergism of smoking and the environment in causing other diseases.

2. It is necessary to determine the threshold, if any, for carbon monoxide with respect to cardiovascular effects, pregnancy, and psychological performance. Carbon monoxide delivery of cigarettes can be controlled by ventilation (66, 126). To determine the carbon monoxide risk of lower "tar" and nicotine cigarettes, we need to know whether thresholds for carbon monoxide activity exist and whether these thresholds vary for individuals of different ages, medical histories, or genetic backgrounds. Evaluation of risk due to carbon monoxide must take environmental exposure into consideration (152).
3. It is necessary to define the extent of smoker compensation for differences in nicotine delivery of cigarettes. To the extent that smokers compensate for lower nicotine delivery, they will probably obtain more of other constituents from lower nicotine than from higher nicotine cigarettes. For example, the smoker might take more puffs to obtain the same dose of nicotine, and thus receive a greater dose of carbon monoxide (80, 145). It should be determined at what point smokers can no longer compensate for lower nicotine levels and whether compensation is a permanent behavior change of smokers who switch to lower "tar" and nicotine cigarettes. To carry out such studies, standardized noninvasive procedures to indicate smoke uptake from cigarettes yielding various amounts of "tar," nicotine, and carbon monoxide should be validated. Analyses of blood, urine, and expired air have been used for these purposes (25, 179, 181). Analysis of saliva for nicotine might also be useful. With any procedure, inter-laboratory comparisons using standardized methods are needed.
4. Many gas phase components of cigarette smoke are ciliotoxic in the experimental setting. They may overcome physiologic defense barriers against pulmonary toxins. To some extent, the ciliotoxic agents are absorbed in the mouth and upper airways and do not reach the deeper portions of the lung. Experimental systems may not be capable of duplicating the anatomic and behavioral factors that may affect human response to ciliotoxic agents. Nevertheless, short-term sequellae of smoking can be measured in human smokers of different types of cigarettes. Further evaluation of these effects in man should be undertaken.
5. Attention to chemical habituation evoked by cigarette smoking is centered on nicotine, which is the most active acute pharmacolog-

ic agent in cigarette smoke. It is necessary to determine whether there may be other chemicals present in cigarette smoke that contribute to cigarette smoking reinforcement.

6. A variety of short-term animal models with quantitative end points predictive of the development of tobacco-associated diseases should be developed. Except for cancer, long-term animal models suitable for quantitative comparisons of disease risk are not adequate. Even if successful long-term animal models are developed, the costs in time and resources may prevent the timely evaluation of new cigarettes.
7. It is necessary to develop methods for dissemination of information regarding the delivery of various noxious agents by cigarettes. The smoke content of "tar," nicotine, carbon monoxide, phenolic constituents, volatile aldehydes, nitrogen oxides, aromatic hydrocarbons, and nitrosamines may all contribute to the risks incurred by smokers. The Federal Trade Commission releases its findings of "tar" and nicotine yields of cigarettes and has announced its intention to assay carbon monoxide delivery. As additional monitoring assays are conducted, it will be necessary to present the new information to the public and to health professionals in a meaningful way.
8. It is necessary to evaluate the health hazard posed by passive inhalation by nonsmokers of the sidestream smoke from new types of cigarettes. Lower "tar" and nicotine cigarettes are designed to reduce the mainstream smoke received by the smoker. There is no evidence that the amount of sidestream smoke or its quality is improved by these design changes. Indeed, if additives are used to insure acceptability of the cigarettes by the smoker, their pyrolytic products may occur in the sidestream smoke. New types of cigarettes should be monitored for the qualitative and quantitative risks they might impose on the nonsmoker.
9. It is necessary to evaluate cigarettes with lower "tar" to nicotine ratios than are currently found in the market place. Compensation by smokers of lower "tar" and nicotine cigarettes appears to be based on nicotine delivery. The "tar" to nicotine ratio may limit the delivery of smoke constituents to the smoker. A low ratio might be a desirable strategy for lower risk cigarettes. It should be determined whether smoke from cigarettes with unusually low "tar" to nicotine ratios has unusual pharmacologic or toxicologic properties.
10. It is necessary to develop a low "tar" and nicotine reference cigarette. Several laboratories will need these reference cigarettes as a standard for comparisons of lower "tar" and nicotine commercial cigarettes. Commercial products cannot serve as a reference because design changes are made without announce-

ment and because the identity of additives is not disclosed. Without a stable reference, intra-laboratory comparisons conducted at different periods of time and many inter-laboratory studies will be compromised. Reference cigarettes are available for a limited range of "tar" and nicotine deliveries. A reference cigarette delivering very low levels of "tar," nicotine, and gas phase constituents is needed. To produce a reference of sufficient quality, large numbers of cigarettes must be made. Because an effort of this magnitude cannot be undertaken by individual researchers, a centralized facility to provide reference cigarettes to appropriate scientists is desirable.

Summary

1. Several thousand constituents have been identified in tobacco and tobacco smoke. Of these, nicotine appears to be the most important acute-acting pharmacologic agent. Nicotine's physiologic effects include increased heart rate and blood pressure. Nicotine also can permit the formation of tobacco-specific nitrosamines, which are potent carcinogens, and nicotine itself may be a significant cocarcinogen. The carcinogenic potency of cigarette smoke condensates appears to depend on the nicotine content of the "tar." This relationship may be due in part to the conversion of nicotine to tobacco-specific nitrosamines or to the coexistence of nicotine and some other unidentified carcinogen. Whether the carcinogenic effects of nicotine as determined in animal studies are directly applicable to humans is not known at present.
2. In an important study to predict the carcinogenic activity of cigarette smoke condensate, the amount of available nicotine delivered to the mice was found to be a factor in every term but one of the predictive model.
3. Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are two prominent classes of tumor initiators found in the smoke condensates of commercial cigarettes. Of the polycyclic aromatic hydrocarbons formed during combustion, benzo[a]pyrene (BaP) may be the most important and has been studied the most extensively. A correlation has been found between benzo[a]pyrene levels and the carcinogenic activity of smoke condensates from several types of cigarettes, but other studies have failed to show that carcinogenic potential is significantly dependent on benzo[a]pyrene content. However, the interaction of BaP with nicotine does appear important in carcinogenesis.
4. The tobacco-specific nitrosamines (TSNA) are formed during curing and fermentation of tobacco leaves and combustion of

- cigarettes. TSNAs induce cancer in the lungs and trachea of hamsters and may be of particular importance in the induction of human laryngeal cancer. They may be active as contact carcinogens, or their metabolism at distant sites may produce carcinogens that are then transported to a target site.
5. It is not known whether the unidentified mutagens in cigarette smoke are an important cause of lung cancer in humans, but added exposure to any tumor initiators probably carries an increased risk of cancer.
 6. Cigarette smoke contains oxidants that have been shown to reduce the activity of alpha₁-antitrypsin in animals and man. This inhibitory function is distinct from the effect whole smoke has on increasing levels of elastolytic enzymes released by neutrophils and macrophages.
 7. The great variety of tobacco types makes it possible to manipulate the plant genetically to change the content of the constituents of the leaf. The chemical content of the leaf is also affected by agricultural practices and curing methods. The nicotine content of tobacco, for example, is related to the amount of nitrate fertilizer used in cultivation. Modification of tobacco as reconstituted sheet incorporates substantial amounts of tobacco stems that contain less nicotine than the leaf. The physical nature of reconstituted sheets can be controlled to change their burning characteristics and smoke composition.
 8. Vapor-phase constituents of cigarette smoke inhibit ciliary motility and mucous flow in experimental animals.
 9. Cigarette smokers metabolize several compounds more rapidly than do nonsmokers. This effect is believed to be caused by the induction of microsomal oxidases, which include aryl hydrocarbon hydroxylase (AHH). Induction of AHH activity appears to be caused by systemic exposure to the smoke compounds themselves or to the metabolites of those compounds. The AHH system may be involved in the metabolic formation of ultimate carcinogens from procarcinogen precursors.
 10. In recent years, a number of flavoring additives or cellulose-based tobacco substitutes may have been included in manufactured cigarettes. The nature and amounts of such additives as actually used are not known, nor is it known what influence these additives may have on the chemical composition or subsequent biological activity of cigarette smoke.
 11. Cigarette design has a major effect on smoke composition. The filter is the design characteristic that has the most impact on "tar" yield; it can also selectively remove nitrosamines and semivolatile phenols from smoke. The porosity of cigarette paper and the presence of holes in the mouthpiece influence smoke

composition because ventilation reduces the quantity of "tar" and dilutes the gas phase of smoke.

12. Because of the complexity of cigarette smoke, the total impact of any cigarette modification on smoke composition will probably never be fully known.
13. Many laboratory studies of the effects of smoke constituents have been carried out using smoking machines that control puff volume, frequency and duration, butt length, and other factors according to standardized parameters. However, the most widely used parameters were established in 1967, and the type of cigarettes generally smoked today are substantially different with respect to length, paper porosity, "tar" and nicotine content, and concentration of gas phase constituents. Evaluation of the toxicological and pharmacological properties of smoke from new types of cigarettes requires detailed knowledge of the manner in which those cigarettes are smoked, as well as of how smoking patterns affect smoke composition.

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