Low-Risk Cigarettes: A Prescription

Low-toxicity cigarettes hold significant promise in the prevention of diseases related to smoking.

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During the last 30 years, epidemiological studies have established that different patterns of cigarette smoking behavior lead to quantitative differences in smoke inhalation and have shown a direct relationship between dose and risk of disease (*1, 2*).

After almost 500 years of experience, smoking has become ingrained in nearly all cultures. As a result of this, two recent decades of antismoking education in our society have met with only partial success: today 55 to 60 million Americans still smoke, and the habit appears to be increasing among teenagers and women (*3*).

For the casual smoker, the kinesthetic and cultural aspects of the habit may be easily forgotten, but for the serious smoker—almost invariably the problem smoker at high risk of disease—the pharmacologic, physiologic, and hedonistic rewards are not easily overcome, even with strong motivation.

Since smoking occupies such a prominent position in the mythology of our daily life, it is unrealistic to expect that a society of nonsmokers could be created after a mere 20 years of public education, particularly in the prevailing sociopolitical climate; historic perspective suggests that many decades may be needed to achieve this goal.

Until then, it is important to protect those who continue to smoke despite all warnings. Leaving them to their fate is neither humane nor economic, particularly when there is evidence that their risk can be reduced substantially in at least two ways.

First, it may be possible to remove toxic smoke components selectively and thus reduce specific hazards. Second, the well-established dose-response evidence suggests that, if the total intake of smoke in the population can be reduced, after an appropriate time a reduction in disease incidence should also occur, as demonstrated for smokers of filter cigarettes (*4*). Many studies (*4–7*) indicate that a combination of these two approaches is feasible, limited only by the market constraints of cigarette acceptability and by the dynamics of taste and perception modification in the consumer.

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Reduction of Toxic Smoke Components

Methods for reducing the smoke yield of cigarettes include genetic selection and low fertilization of plants; growth and harvesting practices that provide "leaner" tobacco leafs; curing methods that remove leaf components; use of high-porosity papers, filters, and smoke dilution devices; and transformation of tobacco into reconstituted sheets through a process that removes undesirable plant components, adds inert diluents, and increases the volume of the original tobacco (*6, 8–15*). Most of these approaches reduce the amount of "fuel" burned during combustion, favor more complete combustion conditions, and discourage pyrolysis, pyrosynthesis, and formation of tar, carbon monoxide, and other undesirable components. In addition, the tar of cigarettes so processed usually shows decreased carcinogenicity when tested on an equal-dose basis against the tar of traditional cigarettes in mouse skin assays (*6, 9, 16, 17*); this is reflected in the steadily decreasing activity of the tars in commercial American cigarettes over the last decade (*18*).

Although nearly 3000 compounds have been identified in cigarette smoke, only a few have been related to specific health hazards. Hydrogen cyanide is considered specifically toxic for the ciliated respiratory epithelium (*19*). The insult of nitrogen oxides may have a role in acute and chronic obstructive pulmonary disease and in the slow development of emphysema (*13, 20*). Various toxic attributes have been ascribed to a number of aldehydes and phenols, acrolein in particular (*6, 21, 22*). The hazard of these components, however, appears small when compared to that of tar, carbon monoxide, and nicotine, except as they affect lung clearance mechanisms. Tar is a mixture of many chemicals and is commonly understood to contain most smoke carcinogens; it also contains other irritants and toxic materials of unidentified properties (*6, 21, 23*). Carbon monoxide is linked to the development of cardiovascular disorders and to acute toxicity phenomena (*24*). The anoxia it produces may precipitate sudden death when an insufficient myocardium is overly stimulated by nicotine (*25*).

Nicotine is recognized as a dangerous alkaloid, but, at the doses delivered by cigarettes, the smoker automatically adjusts intake to favor pharmacologic and physiologic reward (*26*). Except as indicated above—the sudden toxicity of nicotine to a damaged myocardium in relatively anoxic condition—no chronic toxicity effects have been clearly and consistently attributed to nicotine.

Because of its overwhelming pharmacologic contribution, however, nicotine plays an important role in controlling smoking behavior. Within smoke the alkaloid exists in both the protonated and unprotonated forms. The latter form increases with increasing alkalinity of the smoke (*27, 28*) and appears to be more readily absorbed; more important still, it has decidedly satisfying effects on the smoker's taste receptors (*28*). Within certain value ranges, high levels of nicotine, high smoke *p*H values, and high ratios of unprotonated to protonated nicotine increase the satiation effect in the smoker, tend to depress the consumption of cigarettes and the depth and frequency of inhalation (*26, 29*), and therefore reduce the intake of smoke.

Thus it appears that the hazards of cigarettes can be reduced by a simultaneous reduction of tar and of its specific carcinogenic activity; by a reduction of carbon monoxide, nitrogen oxides, hydrogen cyanide, acrolein, and other undesirable toxic smoke components; and by an adjustment of nicotine levels and protonation conducive to consumer satiation.

The technology to achieve these results has been developed and can be applied to the manufacture of commercial cigarettes (*6, 7, 11, 12, 14, 16, 17*). Not surprisingly, such manipulations alter traditional flavor patterns and produce various degrees of conflict with established standards of acceptance. The

Table 1. Daily critical cigarette consumption. Columns 1, 2, and 3 represent the lowest, average, and highest critical values obtained from among all corresponding studies.

Disease mortality	Studies (No.)	Cigarettes (No.)		
		(1) Low	(2) Average	(3) High
Cancer of the oral cavity	3	7–8	8.8	10
Cancer of the pharynx	1	2–3	2.5	2–3
Cancer of the esophagus	2	4–5	7.3	10
Cancer of the pancreas	1	9	9	9
Cancer of the larynx	2	3–4	6.8	10
Lung cancer	10	0.7	5.7	10
Cancer of the bladder and kidney	2	9	9.5	10
Coronary artery disease	3	3–4	4.2	4–5
Coronary heart disease	1	3–4	3.5	3–4
Aortic aneurism	1	4–5	4.5	4–5
Emphysema, bronchitis, or both	1	10	10	10
All causes for current smokers	4	1–2	2	3–4

problem, however, is not insurmountable, because consumer perception can be made to change. For instance, the strength of cigarettes today is nearly half of what it was 15 years ago, when modern cigarettes would have been considered too weak (*30*). There may be lower limits of acceptability, and the success of some new cigarette brands, containing 2 to 8 milligrams of tar and 0.2 to 0.8 milligram of nicotine, indicates that these limits might be quite low. Future commercial cigarettes can be expected to challenge consumer acceptability and to call for cautious marketing policies. These new cigarettes will utilize compensating flavors and fragrances (*31*), and it appears that safety requirements can be met, particularly if added flavors are natural tobacco components, and are little pyrolized or altered during smoking.

Low-Risk Cigarettes

The feasibility of less hazardous cigarettes poses an obvious question: Are there limits of cigarette and smoke composition that may approach relative safety? In pragmatic terms, these limits can be defined as the smoke intake doses at which the risk of disease in smokers is approximately the same as in nonsmokers. Various ways of estimating these values are available—in particular, the dose-response analysis of several epidemiological studies and the extrapolation of blood concentrations at different rates of intake for certain smoke components, such as carbon monoxide.

To derive a dose-response relationship, epidemiological studies associating daily cigarette consumption in males with increases in risk of mortality from 11 specific diseases and of mortality in general were analyzed (*32–44*). A critical value was estimated from each study, this being the maximum number of cigarettes that the average individual could smoke daily without apparently increasing his expected risk of mortality significantly above that of a nonsmoker, within the statistical variation in each study (*45*).

Table 1 summarizes the results of this analysis. The low value is the lowest of all critical values obtained from the studies reviewed; the average and high critical values are defined similarly. The smallest critical value on record is 0.7 cigarette per day for lung cancer; it should be mentioned that this low point is the result of only one study (*32*) of the ten surveyed for lung cancer, the other nine supporting a low value closer to five cigarettes per day.

Most of the studies in this analysis were based on data collected during the 1950's; because the diseases considered have a long latent period, it is fair to conclude that cigarette consumption before 1960 contributed to the risks observed. Table 2 lists the average delivery of some significant smoke components for cigarettes manufactured before 1960 [see also (*6–49*)].

Conservative estimates of upper limits of daily smoke intake should correspond to the lowest intake doses associated with increased risk in epidemiological studies. It could be argued, however, that each smoke component should be judged only in the context of the associated disease; for instance, there is no clear evidence that nicotine is related to lung cancer, but a case could be made for its role in coronary heart disease.

Table 2. Average delivery of smoke components of cigarettes manufactured before 1960.

Smoke component	Average delivery per cigarette
Tar (mg)*	43
Nicotine (mg)*	3.0
CO (mg)†	23
NO_x (μg)‡	270
HCN (μg)‡	410
Acrolein (μg)‡	130

*Sales-weighted averages (*46, 47*). †See (*48, 49*). ‡See (*49*).

At present, the counterargument is more appropriate because the causative attributes of individual smoke components are sufficiently blurred to be of concern. The possible involvement of nicotine in the etiology of lung cancer has not been ruled out; in fact, its indirect role has been suggested by a recent study (*50*).

Thus, a conservative approach suggests using the critical values that apply to all causes of death in smokers. Although "all causes" may include some that are not tobacco related, this comprehensive category represents the effect of cigarette consumption on mortality in general. These critical values are listed in Table 1, and the related critical values of smoke components are listed in Table 3.

Blood concentration of carboxyhemoglobin (COHb) is not directly proportional to CO delivery per cigarette; it is influenced by the smoking and respiration dynamics of the individual and by the number of inhaled puffs that a cigarette delivers. Based on standard considerations (*51, 52*), Table 4 indicates how many cigarettes a smoker could consume daily before reaching critical COHb values, depending on the CO delivery per cigarette.

If the low critical values of the range appear difficult to attain—a smoker could argue that they amount to a nonsmoking prescription—the upper values are in the range of current cigarette marketing and manufacturing realities, although they would necessitate modification of the acceptability requirements of the smoker.

It would be erroneous to interpret these critical values as indicators of safe smoking levels, since the experimental and statistical uncertainties of the studies surveyed are well known, as in most epidemiological work of this kind. Also, regardless of how sophisticated the statistical methods might be, the data should not be interpreted as indicating safe levels, and special provisions would still be necessary for high-risk groups such as coal, uranium, and asbestos workers.

Uncertainty, however, should not be allowed to dilute the implication of these data, namely, that a rapid shift in cigarette consumption habits toward the proposed range of critical values would

make it reasonable to expect that the current epidemic proportions of smoking-related diseases could be reduced to minimal levels in slightly over a decade (*2*). This expectation is plausible because current technology can reduce the specific toxicity of smoke condensate well below the levels prevailing before 1960 (*11, 16, 18*).

All of this evidence is not new, as most of the epidemiological studies reported were completed 10 years ago. It was disregarded, however, for two reasons. The critical values were thought to be too low and beyond manufacturers' capabilities, and there was an ethical conflict with prevailing antismoking attitudes that have recently given way to a more pragmatic approach.

The technology for producing cigarettes, 10 to 20 of which per day deliver smoke within the suggested range, has been developed and can be applied on a mass scale by the skilled cigarette manufacturer. Thus the single most important and potentially successful disease prevention opportunity in contemporary society can be set in motion by responsible marketing decisions in the cigarette industry, by a major public education drive leading smokers to new patterns of acceptance, and by the promulgation of judicious legislative incentives.

Not the least promise of low-hazard cigarettes is that a low delivery of nicotine and smoke will reduce their habit-forming features, and will make it easier for smokers to quit altogether.

Since these approaches are feasible, delays are difficult to justify; the alternative is the continuation of hundreds of thousands of premature deaths and many more disabilities every year.

Summary

Antismoking education campaigns in our society have met with only partial success: today 55 to 60 million Americans smoke, and the habit is increasing among teenagers and women. It is important to protect individuals who continue to smoke despite all warnings. There is evidence that this can be accomplished in at least two ways.

First, it may be possible to remove toxic smoke components and thus reduce specific hazards. Second, the dose-response evidence suggests that, if the total intake of smoke can be reduced, after an appropriate time a reduction in disease incidence should occur. The technology to achieve these results has been developed and can be applied to the manufacture of commercial cigarettes. These cigarettes will not conform to traditional flavor patterns, but consumer perception can be made to change and compensating flavors and fragrances can be added.

The feasibility of less hazardous cigarettes raises the question of whether there are limits of cigarette and smoke composition that may approach relative safety. These limits can be defined as the smoke intake doses at which the risk of disease in smokers approaches that in nonsmokers. Such values can be estimated by dose-response analysis of several epidemiological studies and by extrapolation of blood concentrations at different rates of intake for certain smoke components, such as carbon monoxide. Critical values determined by these methods should not be interpreted as indicators of safe smoking levels; they do imply, however, that a rapid shift in cigarette consumption habits toward the proposed range of values will make possible a substantial reduction in the current epidemic proportions of smoking-related diseases.

Table 3. Critical values of daily intake of selected smoke components based on data associated with all causes of disease mortality for current smokers. For COHb, critical values are expressed in terms of the percentage increase of COHb in the smoker's blood, as described in (*57*). For the remaining components, the critical values listed in Table 1 for "all causes for current smokers" were multiplied by the corresponding average deliveries of smoke components listed in Table 2 to obtain critical values in terms of smoke components.

Smoke component	Critical values		
	(1) Low	(2) Avg.	(3) High
Tar (mg)	65	86	151
Nicotine (mg)	4.5	6.0	10.5
COHb (increase, %)	2.6	3.2	4.8
NO_x (μg)	405	540	945
HCN (μg)	492	820	1435
Acrolein (μg)	156	260	455

Table 4. Daily cigarette consumption needed to reach critical COHb levels, as a function of CO delivery per cigarette. It is assumed that the consumption of cigarettes is evenly spaced over a 10-hour period; see (*51*).

CO delivery per cigarette (mg)	Daily cigarette consumption		
	Low critical value	Average critical value	High critical value
2	19	22	35
5	8	10	16
10	4	5	7
15	2	3	5
20	2	2	4

References and Notes

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32. Four source documents contained summaries of the data used to compute the critical values of daily cigarette consumption. Following is a list of these documents, the studies within each document that were used to compute the critical values, and the results of the computations.

1) From "Smoking and health, report of the Advisory Committee to the Surgeon General of the Public Health Service" [*U.S. Public Health Serv. Publ. 1103* (1964), pp. 89 and 324], the total age-adjusted critical value (CV) for mortality from coronary heart disease for males (*33*) was 3 to 4; for mortality from all causes for male current smokers, CV was 1 to 2 in a study of men in nine states (*33*), 1 to 2 in a study of U.S. veterans (*34*), 3 to 4 in an occupational study in California (*35*), and 2 to 3 in a study of men in 25 states (*36*); and for mortality from coronary artery disease for males, CV was 4 to 5 for men in nine states (*33*), 3 to 4 for U.S. veterans (*34*), and 4 to 5 for men in 25 states (*36*).

2) From "The health consequences of smoking, a Public Health Service review: 1967" [*U.S. Public Health Serv. Publ. 1696* (1968), pp. 69, 93, 140, 146, 157, and 184], CV was 4 to 5 for cirrhosis of the liver, > 10 for cancer of the buccal cavity, 2 to 3 for cancer of the pharynx, and 4 to 5 for aortic aneurism in U.S. veterans (*37*); > 10 for emphysema, bronchitis, or both in Canadian pensioners (*38*); and 7 to 8 for lung cancer in males in Northern Ireland (*39*).

3) From "The health consequences of smoking, a report to the Surgeon General: 1971" [*DHEW Publ. (HSM) 71-7513* (1971), pp. 241–243, 286, 290, 294, 298, and 359], CV was 4 to 5 for esophageal cancer, > 9 for both pancreatic and oral cavity cancer, 3 to 4 for cancer of the larynx, > 9 for kidney and bladder cancer, and 1 to 2 for lung cancer in U.S. veterans (*37*); 0.7 for lung cancer in males from 25 states (*36*); 7 to 8 for lung cancer in males from nine states (*33*); 4 to 5 for lung cancer in British physicians (*40*); > 10 for lung cancer in American Legion males (*41*); 4 to 5 for lung cancer in California males (*42*); and > 10 for lung cancer in Japanese males (*43*).

4) From *Epidemiology of Tobacco-Related Cancers with Special Emphasis on the Effect of Lower Tar Cigarettes* (American Health Foundation study, 1969–1975, in press), for males CV was 2 to 3 for Kreyberg type I lung cancer, 8 to 9 for Kreyberg type II lung cancer, 7 to 8 for cancer of the oral cavity, > 10 for cancer of the larynx, > 10 for esophageal cancer, and > 10 for cancer of the bladder.
33. White American males enrolled by the American Cancer Society in nine states [E. C. Hammond and E. C. Horn, *J. Am. Med. Assoc.* **166**, 1159 (1958); *ibid.*, p. 1294].
34. Veterans who served between 1917 and 1940 and were policyholders of U.S. government life insurance policies [H. F. Dorn, *Proc. Soc. Stat. Sect. Am. Stat. Assoc.* (1958), pp. 34–71].
35. Men 33 to 64 years old in nine occupations in California [J. E. Dunn, Jr., G. Linden, L. Breslow, *Am. J. Publ. Health* **50**, 1475 (1960)].
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43. T. Hirayama, *Smoking in Relation to the Death Rates of 265,118 Men and Women in Japan* (National Cancer Center, Research Institute, Epidemiology Division, Tokyo, September 1967).
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45. It is not possible to directly compare the epidemiological studies considered, because they differ with respect to design, quality of data, demographic characteristics, and numbers of subjects surveyed (*32*). Thus, each study was initially analyzed separately. For each study the data may be typified by the relative risk associated with the number of cigarettes consumed daily; for example, for no cigarettes the relative risk value is 1.00; for 1 to 10 cigarettes, 5.49; for 11 to 20 cigarettes, 9.91; for 20 to 39 cigarettes, 17.41; and for > 40 cigarettes, 23.93. For some studies, the categories of daily cigarette consumption differed from these.

The first step in the analysis was to fit the data to a function of the form

$$R = A_0 + A_1X + A_2X^2 \qquad (1)$$

where R denotes the relative risk value; A_0, A_1, and A_2 are coefficients whose values were calculated by the statistical method of maximum likelihood; and X is the daily cigarette consumption. Since the available daily cigarette consumption data were expressed as intervals (1 to 10, 11 to 20, and so on), the upper bound of each interval was used in the calculations. Thus, for the example above, the interpretation is that a daily consumption of at most 10 cigarettes has an associated relative risk of 5.49, a daily consumption of at most 20 cigarettes has an associated relative risk of 9.91, and so forth. When the highest daily consumption value was expressed as an open-ended interval, such as > 40, the value used was arbitrarily set at 10 more than the value specified. In the example above, 50 was used for the highest daily consumption.

Although other functions were considered, graphical observation and statistical analysis suggested that the quadratic function (Eq. 1) provides an exceptionally good fit to experimental data such as those considered here. For example, the corrected multiple coefficient of determination in each case was greater than 0.90.

For the example we are considering, Eq. 1 becomes

$$R = 1.388 + 0.393X + (0.993 \times 10^{-3})X^2 \qquad (2)$$

The next step in the analysis was to calculate, for each study, the least significant difference between 1.00 (the relative risk for a nonsmoker) and the estimated relative risks for a daily cigarette consumption of 1, 2, . . ., 10 cigarettes. Estimated relative risks were computed from Eq. 1. The number of cigarettes corresponding to this least significant difference was then interpreted as the critical value. For our example, and using Eq. 2, the critical value lies between 1 and 2 cigarettes per day.

The least significant difference depends, of course, on the level of significance chosen. For this analysis, the statistical power is more important than the level of significance. That is, it is more important that any attendant error lead to a lower rather than a higher critical value. Consequently, the level of significance was set at 10 percent, rather than at the more frequently used values of 5 percent or 1 percent to increase power.

This methodology was applied to each of the studies listed in (*32*), leading to the values shown in Table 1.
46. Tars and nicotine in the smoke of 64 brands of cigarettes [*Consumer Reports* (April 1961), p. 206].
47. Sales figures used in this study were as reported in *Tobacco* (14 February 1964), p. 13.
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50. F. G. Bock, *Proc. Am. Assoc. Cancer Res.* **17**, 2 (1976).
51. With a postexposure decay factor of $(0.85)^{t'}$ (*44*), the increase in percentage of COHb in the blood of inactive young men due to smoking (*52*) is given by

$$\text{Percent COHb increase} = [(\text{CO})^{0.858}t^{0.63}/197] \times 0.85^{t'} \qquad (1)$$

where CO is expressed in parts per million (ppm), t is the exposure time in minutes, and t' is the postexposure time in hours.

The mean CO delivery during smoking depends on the CO delivery of the cigarette, the smoking period t, and the volume of inspired air. The maximum CO delivery of a cigarette is related to CO concentration (ppm) by

$$\text{CO} = C_{\text{CO}}RT \times 10^6/R_vVM_{\text{CO}}t \qquad (2)$$

where C_{CO} is the CO per cigarette (mg), R is the ideal gas constant (liter-atm deg^{-1} mole^{-1}), R_v is the ventilation rate (min^{-1}), V is the volume inhaled per ventilation (cm^3), M_{CO} is the gram molecular weight of CO, T is the temperature (absolute), and t is the smoking period.

With $R = 0.0821$ liter-atm deg^{-1} mole^{-1}, $T = 298$°K, $R_v = 22$ min^{-1} (a lower ventilation rate during the smoking period would lead to higher COHb levels), and $M_{\text{CO}} = 28$ g/mole, Eq. 2 reduces to

$$\text{CO} = 79.43C_{\text{CO}}/t \qquad (3)$$

Combining Eqs. 1 and 3 gives

$$\text{Percent COHb increase} = [0.2166{C_{\text{CO}}}^{0.858}/t^{0.228}] \times 0.85^{t'} \qquad (4)$$

The increase in the percentage of COHb immediately after smoking the last cigarette in a series of N equally spaced cigarettes, each smoked over a 5-minute period, is thus given by

$$\text{Percent COHb increase} = 0.1501{C_{\text{CO}}}^{0.858} \sum_{t_i=0}^{t'} 0.85^{t_i} \qquad (5)$$

Equation 5 was used to estimate the increase in percentage of COHb immediately after smoking the last cigarette in a 10-hour smoking session. The CO yield was taken as 23 mg per cigarette (typical pre-1960 cigarette), and the numbers of cigarettes smoked were the same as the critical values for "all causes for current smokers" listed in columns 1, 2, and 3 of Table 1. Thus, these critical values were expressed in terms of the percentage COHb increase for a 10-hour smoking session, and the COHb values are given in Table 3. Next, the numbers of cigarettes producing the same percentage changes in COHb, but delivering 2, 5, 10, 15, and 20 mg of CO per cigarette, were computed. Thus, the critical values (Table 1) based on a cigarette delivering 23 mg of CO were converted to critical values based on cigarettes delivering varying amounts of CO through the intermediary of percentage COHb increase in the smoker. The results are listed in Table 4.
52. J. E. Peterson and R. D. Stewart, *Arch. Environ. Health* **21**, 165 (1970).