Carboxyhemoglobin in Relation to Smoking

THEODORE J. CURPHEY, *M.D.*,[1] *Chief Medical Examiner—Coroner, Los Angeles County, Los Angeles, California 90012*

THE main thrust of the Conference and the tenor of discussion in the general sessions and in this workshop have been to review and analyze the various agents in tobacco smoke with regard to their potential threat to the health and well-being of the cigarette smoker. The evidence already presented has dealt largely with those effects of certain components of tobacco smoke as they relate to such problems as myocardial infarction, blood coagulation, and carcinogenesis. What can be done to reduce such hazards as "tar" and nicotine, thus leading to the production of a less harmful cigarette, has been discussed.

This afternoon's workshop seems to me to be a variation on the general theme, being in the nature of a movement written in a minor key. It has dealt with certain components in tobacco smoke, *e.g.*, nicotine, whose deleterious properties have not been experimentally and clinically established, but which are nevertheless under various degrees of suspicion. Therefore, these components must be examined in the process of writing the score for the orchestration of Dr. Wynder's symphony, entitled *Toward a Less Harmful Cigarette.*

Carbon monoxide (CO) is one of these components of tobacco smoke that has long been suspected of being harmful and, hence, has received much study over the years.

The problem of CO as a harmful constituent of tobacco smoke raises two questions:

1. Does the amount of CO in the blood differ between the smoker and nonsmoker?
2. If more CO is present in the blood of the smoker, does it produce either functional or structural pathological changes? Are such changes demonstrable by symptomatic, clinical, or laboratory evidence, and can they therefore be assumed to be detrimental to the health or well-being of the smoker as is true in the case of other components of tobacco smoke?

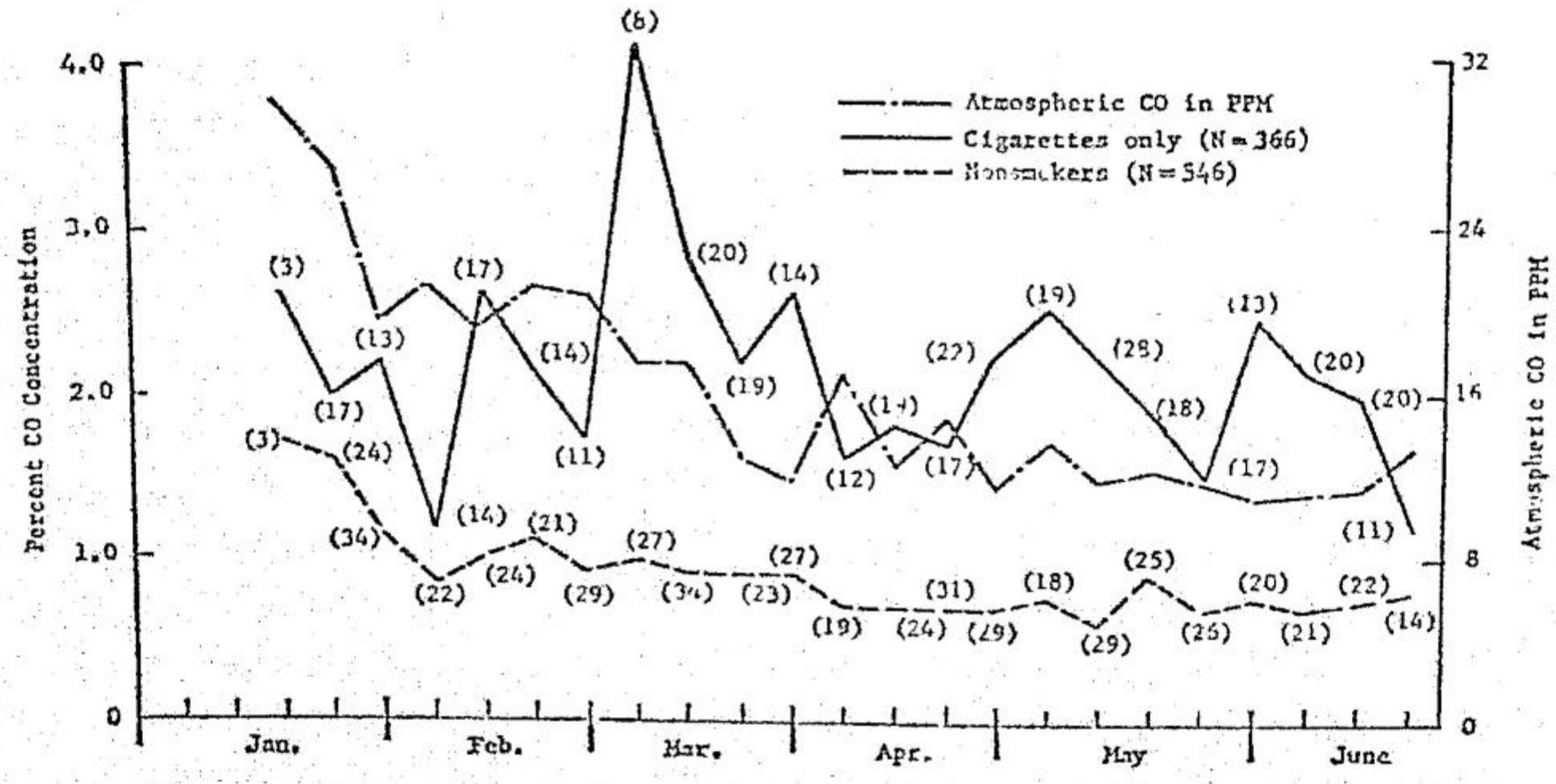
There is abundant evidence in the literature to answer unequivocally the question of the difference between the CO blood level concentration in the

[1] Retired. *Present address:* 1344 Wellington Ave., Pasadena, Calif. 91103.

smoker and nonsmoker. The article by Larson *et al.* (*1*) is replete with references covering studies over the past 50 years of CO blood levels in smokers and nonsmokers under various conditions, as well as the effect of various quantity levels of smoking on the CO blood level.

Numerous studies on the normal blood level of CO in the nonsmoker show ranges from 0.5–2.8%. In our study, we used 1% as the normal level.

The data to be presented on the amount of CO in the blood of smokers are a good example of serendipity. Originally our study was aimed at determining whether there was any correlation between the postmortem CO blood levels of individuals handled by the Los Angeles County Medical Examiner's Office and the CO level of the ambient air at the time of death. We were not considering the cause or mode of death, but were looking for a way to use the CO blood level as a daily indicator of air pollution in the Los Angeles basin (text-fig. 1).



TEXT-FIGURE 1.—Distribution median of CO in blood of cigarette-only smokers and nonsmokers.

After analyzing our data, we observed a significant association, which, however, was not noted for every location of the monitoring station. Goldsmith *et al.* (*2*) who had studied the blood CO levels of longshoremen in San Francisco in relation to their smoking habits suggested that the collected data be used to study the smoking habits of this postmortem population.

From November 1–June 30, 1961, 2,207 cases were surveyed, and the data were correlated with 1) the CO concentration of the ambient air at certain monitoring stations in Los Angeles and 2) the smoking habits of the study group (*3*). To determine the smoking habits of the group, a questionnaire was mailed to the next of kin, when known, or to a known informant. This reduced the group to a total of 1,878 persons, from whom we received usable smoking histories for 1,078 persons.

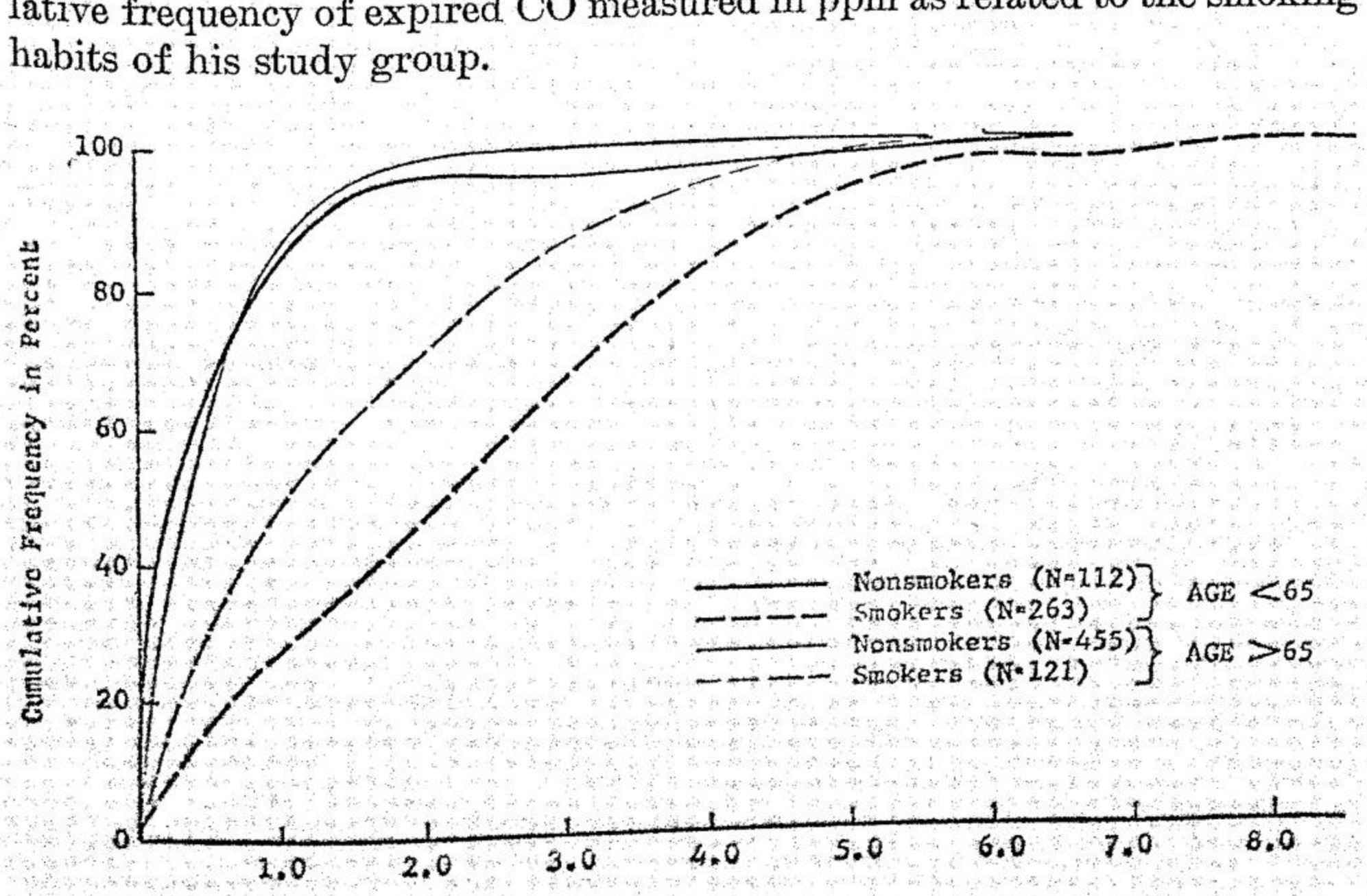
The 1,078 persons were divided into two groups: 1) nonsmokers (including ex-smokers and persons who never smoked), and 2) smokers. These

two groups were further subdivided into (*a*) those under age 65 and (*b*) those over age 65. The blood CO levels in the entire group ranged from 0–11.6%. Over 80% of the nonsmokers, regardless of age, fell in the 1% or less CO level. A blood CO level of 5%, regardless of smoking habit, was considered abnormally high.

Forty-six persons had values of 5% and all of these were smokers, except 3 who were ex-smokers. Only 7 of the 46 persons were age 65 or over; in other words, 85% of the persons were in the younger age group. Furthermore, with the use of 1% CO as the normal blood level for nonsmokers, 62% of the nonsmokers had less than this level, whereas only 22% of the smokers had values this low (text-fig. 2). Also, the smokers tended to have a much greater frequency at the extreme values of more than 4%. Moreover, smokers over 65 years old had almost twice as high a percentage value under 1% as the smokers under 65 years (text-fig. 2). The interpretation of this finding offers room for speculation, with one possibility being that older smokers might smoke less than their younger counterparts.

Another interesting fact gleaned from a study of the observed median CO values is that the values of male nonsmokers were greater than those of female nonsmokers by a factor of nearly 2. On the other hand, for smokers, the distribution by sex did not show consistent differences.

That there is a direct correlation between the height of the CO blood level and the number of cigarettes smoked is a well-established fact, as demonstrated by Goldsmith (*2*) in his study of a group of San Francisco longshoremen (text-fig. 3). This is seen in the graph of percentage cumulative frequency of expired CO measured in ppm as related to the smoking habits of his study group.



TEXT-FIGURE 2.—Percentage cumulative frequency and percentage of blood CO in smokers and nonsmokers.

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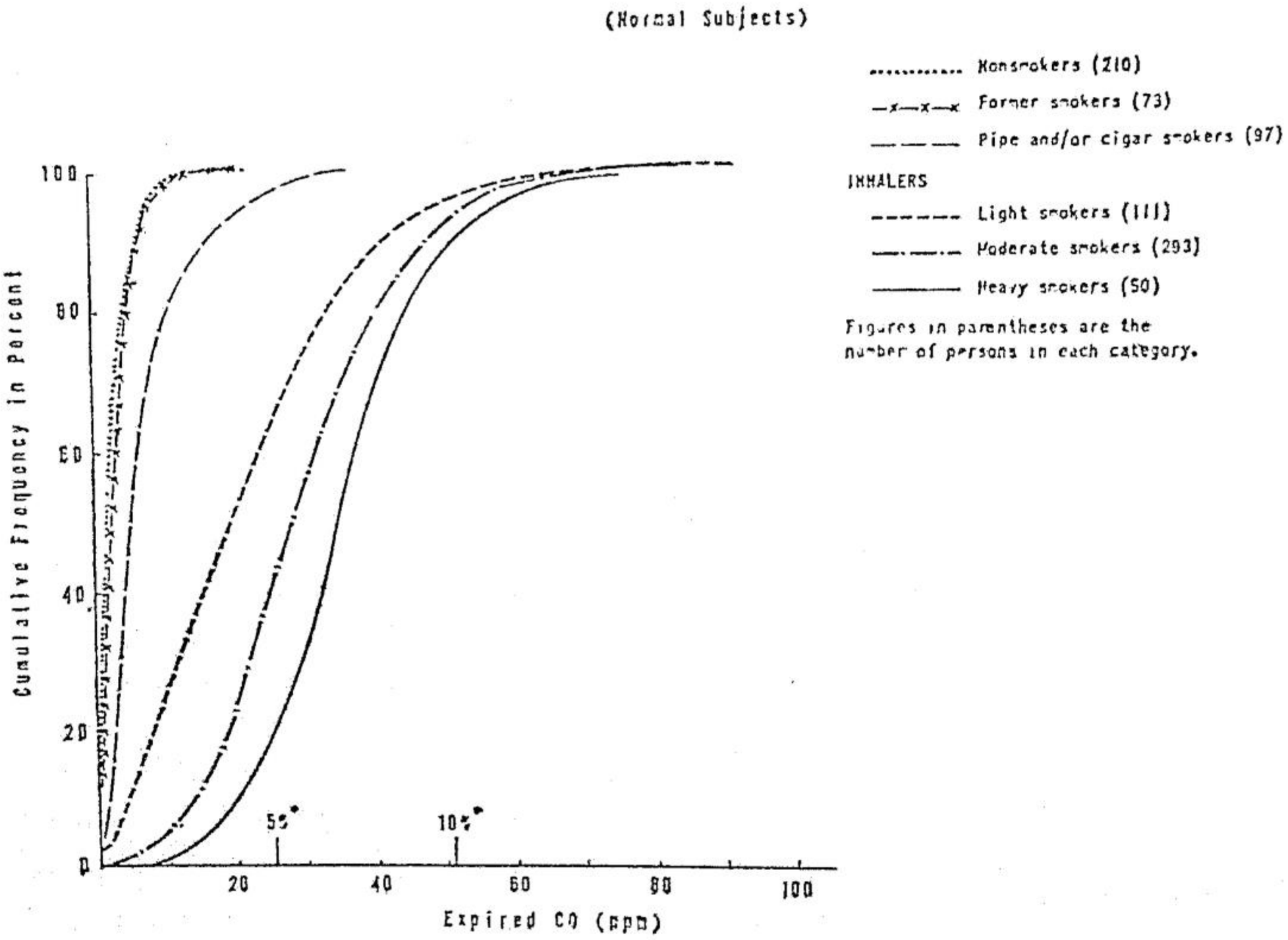

TEXT-FIGURE 3.—Distribution of expired CO in longshoremen, by smoking pattern: ILWU study, 1961. *Percent carboxyhemoglobin concentration based on regression: COHb% = 0.21 + 0.19 × (CO ppm).

The graphs of Goldsmith's cases of live persons and of our cases show very good correlation in the CO expressed in ppm of expired air with that obtained from a study of postmortem blood expressed in percentage terms of carboxyhemoglobin concentration.

Goldsmith did not correlate the CO blood levels with the general health of his subjects; and obviously in our series, we were denied that opportunity, since the deaths we studied included those from natural causes due to disease and also homicidal, suicidal, and accidental deaths. In point of fact neither of these studies answers the question "Is smoking dangerous to health?"

Fortunately, there is good evidence available which bridges this gap, namely, the study made by Sievers *et al.* (*4*) of the effect of exposure to known concentrations of CO on a group of 156 police traffic officers, between 32 and 51 years old, who were assigned to duty in the Holland Tunnel for a period of 13 years. These officers were exposed to an average of 70 ppm of CO, which is equivalent to 10% (COHb saturation), with brief exposures up to 200–300 ppm at times and with the heaviest level for a 24-hour period of 86 ppm (14% COHb). Infrequently, the CO level exceeded 200 ppm (32% COHb) and rarely rose as high as 300 ppm (40% COHb) for a few minutes at a time.

This study on police traffic officers is particularly valuable for the purpose of this workshop, for it demonstrated that these men showed no

evidence of injury to their health, as determined by serial physical examinations, blood and urine studies, EKG tracings, blood pressure readings, and neurological examinations. In this latter connection, an excellent test for judging the integrity of the nervous system was the pistol marksmanship record of these officers. The Port Authority pistol team was composed of 7 officers, 6 of whom had tunnel duty, and the team consistently finished in first or second place in formal competition with pistol teams from other police organizations for 7 consecutive years.

Even more pertinent to our charge at this time is the study of the smoking habits of the officers in relation to their blood CO levels. Variation in the entire group ranged from 0.5–13.1% saturation, the highest values being obtained in those who smoked and were stationed on the upgrade section of the tunnel and who were exposed to atmospheric CO readings slightly above 100 ppm (16% COHb saturation) for a 2-hour period in contrast to the average daily value of 70 ppm (10% COHb saturation).

What appears to be the most significant observation in this study of traffic officers in the Holland Tunnel is that the blood CO levels of nonsmokers in the tunnel on the average exceeded those of smokers in an environment free from any occupational exposure to CO. Since these men remained healthy after being consistently exposed for 13 years to CO levels appreciably higher than those found in tobacco smoke, the conclusion then is inescapable that smokers with CO levels that lie well within these same ranges are similarly unaffected by CO.

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Selective Removal of Components of Tobacco Smoke by Filtration[1]

T. Waller George, *North Carolina State University, Raleigh, North Carolina 27607*

THE smoke yield from cigarettes is a complicated substance containing a number of physical states of matter. On one hand, there are low-boiling molecular species in smoke which vary considerably in molecular weight (*e.g.*, materials such as water and extending to relatively complex equally volatile organic molecules). Many of these are probably present in the smoke stream as fairly typical real gases. On the other hand, there are more or less well-defined aerosol particles varying from liquid to solid. In some instances the aerosol particle contains a solid core and is surrounded by a well-defined liquid layer; in others, the aerosol probably approximates a classical liquid drop. In particles met in freshly formed, diluted smoke, the diameters have been estimated to lie between several hundredths of 1 μ for the very smallest to 1 μ. As produced by the tobacco combustion process, between 10^8 and 10^{10} particles exist in each cm^3 of freshly formed smoke. The particulate material including water from all sources constitutes about 10% of the weight of all material in a puff of cigarette smoke. Typically the weight of the aerosol matter is of the order of 50 mg per cigarette when cigarettes are smoked in standard fashion with mechanical smoking machines. The weight of all matter in the puff, which usually is inhaled by a cigarette smoker, is approximately 500 mg per cigarette. It is composed principally of the permanent gases of air, namely, oxygen, nitrogen, and carbon dioxide.

At the time real smoke streams enter the filter, much of the smoke substance is not in thermal or chemical equilibrium, but is moving in and out of the aerosol phase of the smoke. This unstable matter may be termed "volatile." This material is condensable in appropriate traps and is probably completely gaseous for measurable times after formation in the com-

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[1] This manuscript contains material selected from a paper by the author and C. H. Keith entitled "The Selective Filtration of Tobacco Smoke," chapter XI, in *Tobacco and Tobacco Smoke* by E. L. Wynder and D. Hoffmann, published by Academic Press Inc. The reader should consult this paper for detailed references and additional information.

bustion zone. Later, as it enters the filter, the bulk of the volatile substances is probably in the form of precondensation nuclei of quite small dimensions intermediate between molecular and aerosol.

Both the volatile materials and aerosols exist in the smoke stream as products of the combustion. Some volatile clusters doubtless grow through collision into bona fide aerosols while others, due to the unstable nature of the mixture which composes the particle, disintegrate into the gaseous stream.

Concerning direct observation, relatively little can be said about the true physical nature of the volatile components of cigarette smoke. Their chemical identity clarifies their equilibrium properties. Their physical state in fresh smoke is probably best postulated. The physical reasonableness of such postulates is at least intuitively satisfying if one observes that many components known to exist in smoke condensate are of such a nature as to exhibit boiling points well below the mean sensible smoke stream temperature when it enters the filter; that is, a temperature from 5–10 degrees above ambient.

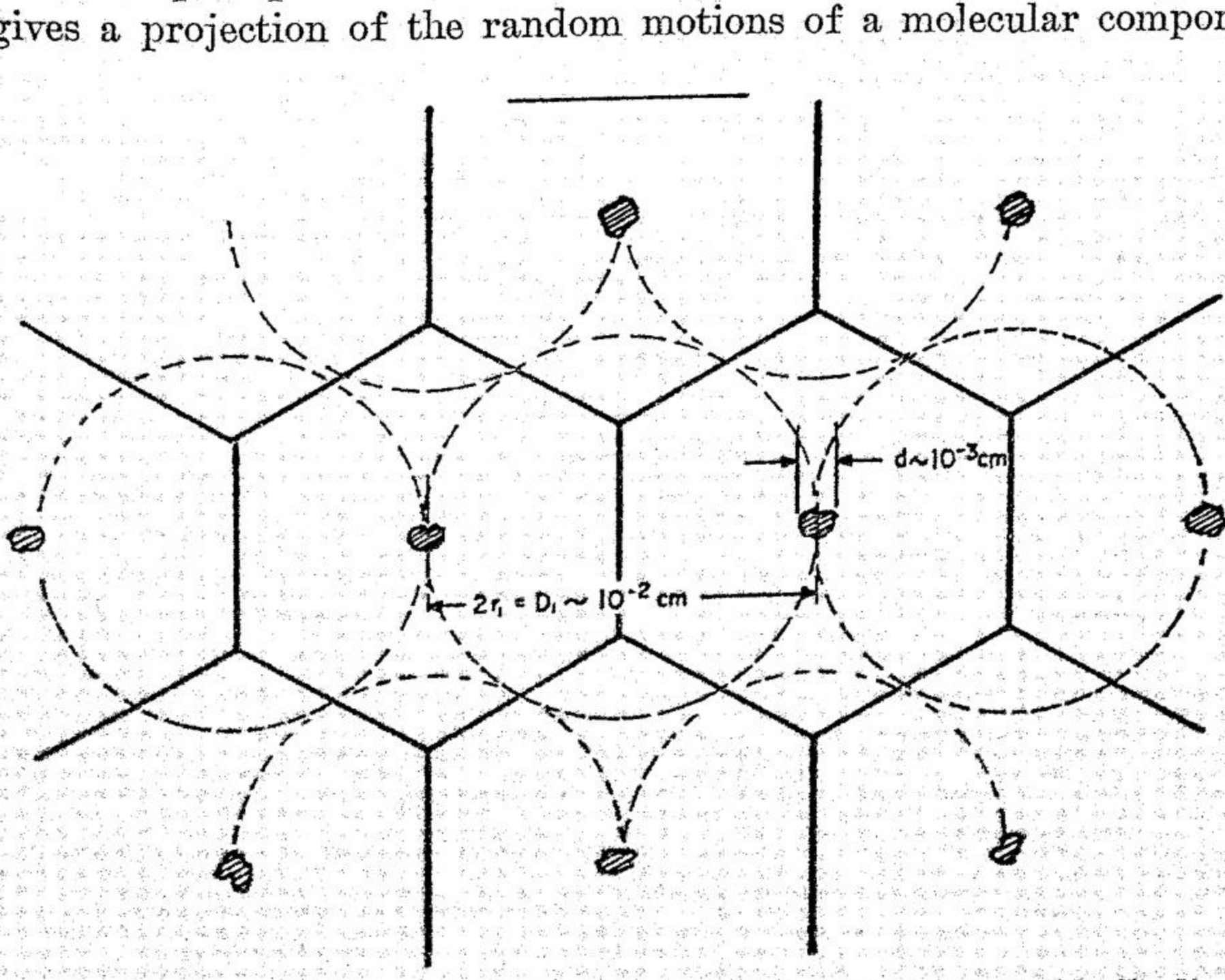
The primary combustion zone for a cigarette is an annular ring surrounding the coal. Most air drawn past the coal moves through this ring. Some air enters the smoke column through the unburned, porous cigarette paper. This air dilution represents a considerable fraction of the main stream smoke and in certain cigarettes is further enhanced by purposefully added perforations located near the tobacco end of the filter overlay. These perforations superficially reduce the condensable and particulate material in the mainstream smoke by effectively permitting much of the inhaled puff to be derived from air that does not pass through the annular combustion zone. This device to reduce the amount of combustion products in the inhaled stream is one practical means of control of the amount of condensable smoke. It probably alters the stability of the smoke aerosol and volatile substances tending to quench these in a state more typical of the one with which they left the combustion zone. One might anticipate slight increases in the amount of volatile material in this case.

The mainstream smoke moves relatively slowly through the tobacco column and enters the cigarette filter. When Reynolds numbers computed on the basis of shred-to-shred distances are used, it is possible to estimate that smoke moves in largely laminar fashion, since critical values of Reynolds numbers in channels usually are observed to be of magnitudes higher than those estimated for the cigarette case. A more realistic critical Reynolds number with which to compare estimated values can be based on observation of fluid flow through porous media. The critical Reynolds numbers characteristic of such flows range in order of magnitude on either side of unity for media having a porosity somewhat lower than that typically found in the cigarette filter or the tobacco column. Measurements for critical flows in lower porosity media are not available. However, if such critical values are taken as intuitively plausible for the lower

porosity structures of real cigarettes, one may conclude that there is a possibility that the fluid flow through the filter of mainstream smoke contains significant turbulent components.

The character of the obstacles which the smoke stream passes in the cigarette filter is generally of two types. The structure of most commercial filters contains internal surfaces largely parallel to the axis of the cigarette. A second class of surface is essentially normal to that axis. Those filters made primarily from textile fibers partially aligned parallel to the axis of the cigarette possess quite open cross sections. These open channels are characteristically sinuous due to the deregistration of the crimp that is accomplished during filter manufacture. The smoke stream is swept along these open channels and impinges at angles varying from grazing incidence to perhaps 30 degrees to the normal of fiber component. The fluid moving between the fiber elements contains irregular motion quite analogous to normal Brownian motion. Much of the mean motion is a smooth, laminar, or potential flow which sweeps smoke components past the filter elements. In addition, this author believes that a significant amount of microturbulence exists in the flow which further increases the probability of mechanical contact between smoke substances and the filter elements. This microturbulence is caused by the prior unstable flow around the coal and through the tobacco column.

Text-figure 1 shows a typical cross section of a man-made textile fiber filter drawn approximately to the proper geometric scale. The large amount of open space mentioned previously is clearly visible. Text-figure 2 gives a projection of the random motions of a molecular component



TEXT-FIGURE 1.—Local cross-sectional geometry of cigarette filter (idealized).

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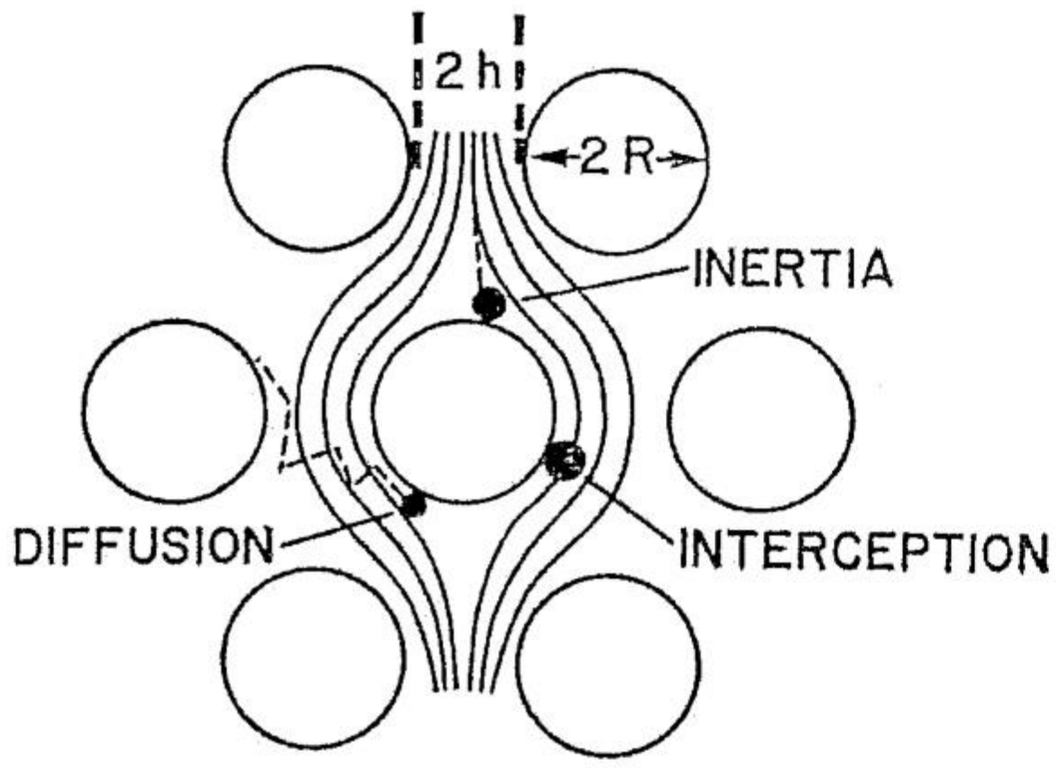
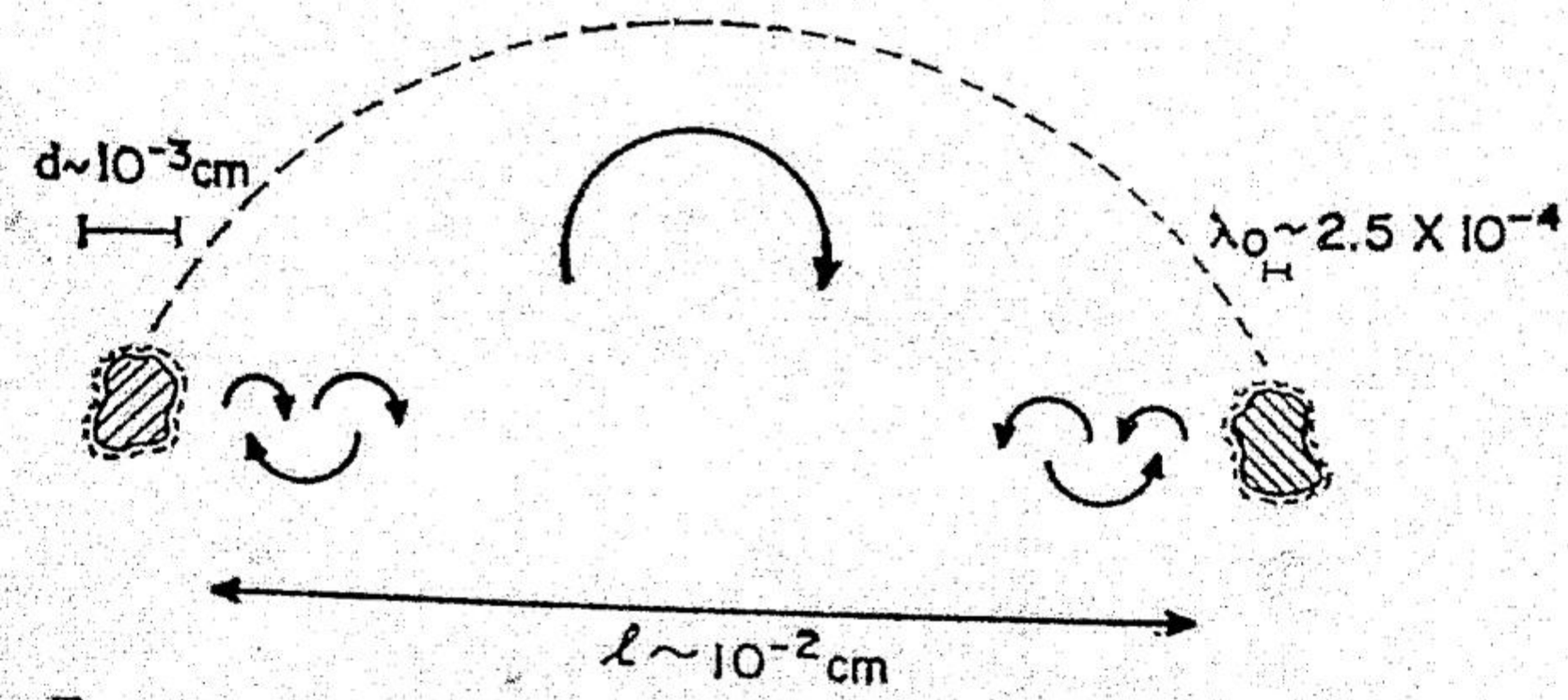


TEXT-FIGURE 2.—Projection of the random motions of a molecular component of smoke stream due to Brownian movement of streams past filter fiber cross section.

of the smoke stream that are experienced due to Brownian movement of streams past the filter fiber cross section. Text-figure 3 exhibits a conception of the microturbulence which may be present within this smoke stream and which arises within it as the smoke is drawn through the coal and the various porous openings along the cigarette length.

Many practical cigarette filters contain fibrous and particulate additives that are intermingled among the filter fibers. In other instances, the filters are composed of sections, one of which contains a bed of particles or similar structures. These provide additional resistance to motion in the open channels and increase the probability of mechanical filtration as well as enhance the amount of surface available for sorbing components which prefer to exist on the surface elements of the filter rather than within the primary smoke stream.

Fine fibers represent physical structures which exhibit an extremely high sensitivity to their molecular environment. At the molecular level and slightly above it, the fiber structure is relatively porous and possesses a large capacity to exhibit surface sorption phenomena. Both gaseous and



TEXT-FIGURE 3.—Conception of the microturbulent motion (schematic).

denser fluids, possessing affinities for the fiber structure, move rapidly through these complexes of surfaces once the fiber is exposed to them.

It is perhaps instructive to indicate to order of magnitude how rapidly such a movement occurs, since it is indeed significant. One may estimate the time it takes for a gaseous substance or a liquid substance with affinity for a fiber to be sorbed to a concentration within a fiber that is 80% of the equilibrium value from the following formulas:

$$Kt/R^2 = 0.2 \quad \text{or} \quad t = 0.2\ R^2/K. \qquad [1]$$

In the above formulas the fiber is compared to a long cylinder of radius R; t is the time for 80% of the surrounding medium with affinity for the fiber to reach the equilibrium concentration within the fiber; and K is the diffusion coefficient for the diffusing material within the fiber.

Values for the diffusion coefficient for water in some fibers range from 10^{-3} cm^2/second to 10^{-7}. When water diffuses through hydrogen-bonded substances, the latter value is more typical. For a fiber with radius of 10^{-3} cm (a fairly typical filter fiber), the above formula suggests that concentration buildup to 80% of equilibrium value would occurr in approximately 2 seconds. Other substances will give similar orders of magnitude. Since the duration of a typical puff is 2 seconds, one may readily say that, if the affinity between the filter media's surface and the given smoke component is fairly high, there will be time for a significant portion of the component to be sorbed onto the surface of the media. This is the basis of selective sorption in the filtration of cigarette smoke. The problem in a technological sense arises from the requirement that the interesting smoke component be volatile and that the filter be manufactured with sufficiently high amounts of surface to provide for sorption.

An interesting extension of the above formula can be made to the fibrous organelle, the cilium, which lies in the epithelium of the bronchial tree as well as in the nasal cavities. In man these cilia may have a radius of approximately 10^{-6} centimeters. Again, if water is used as a substance to be diffused and a diffusion coefficient typical of keratin, using the equation given above, Astbury calculated many years ago that 80% equilibrium would be reached within a cilium in approximately 10^{-5} seconds. This computation provides one with a ready means for understanding the essentially instantaneous reactions that have been produced in ciliated tissue sections exposed to tobacco smoke. Stasis is nearly instantaneous. A similar argument can be developed for the interaction between smoke components and taste buds resulting in extremely short times required to register the effect of smoke components within the taste receptor.

We see, thus, that the physiology of interaction of tobacco smoke with tissue components is quite similar to the reaction with filter media possessed with affinity for the smoke component. The smaller the diameter of the reacting surface, the faster the reaction; the larger the total amount of surface, the greater the amount of reaction.

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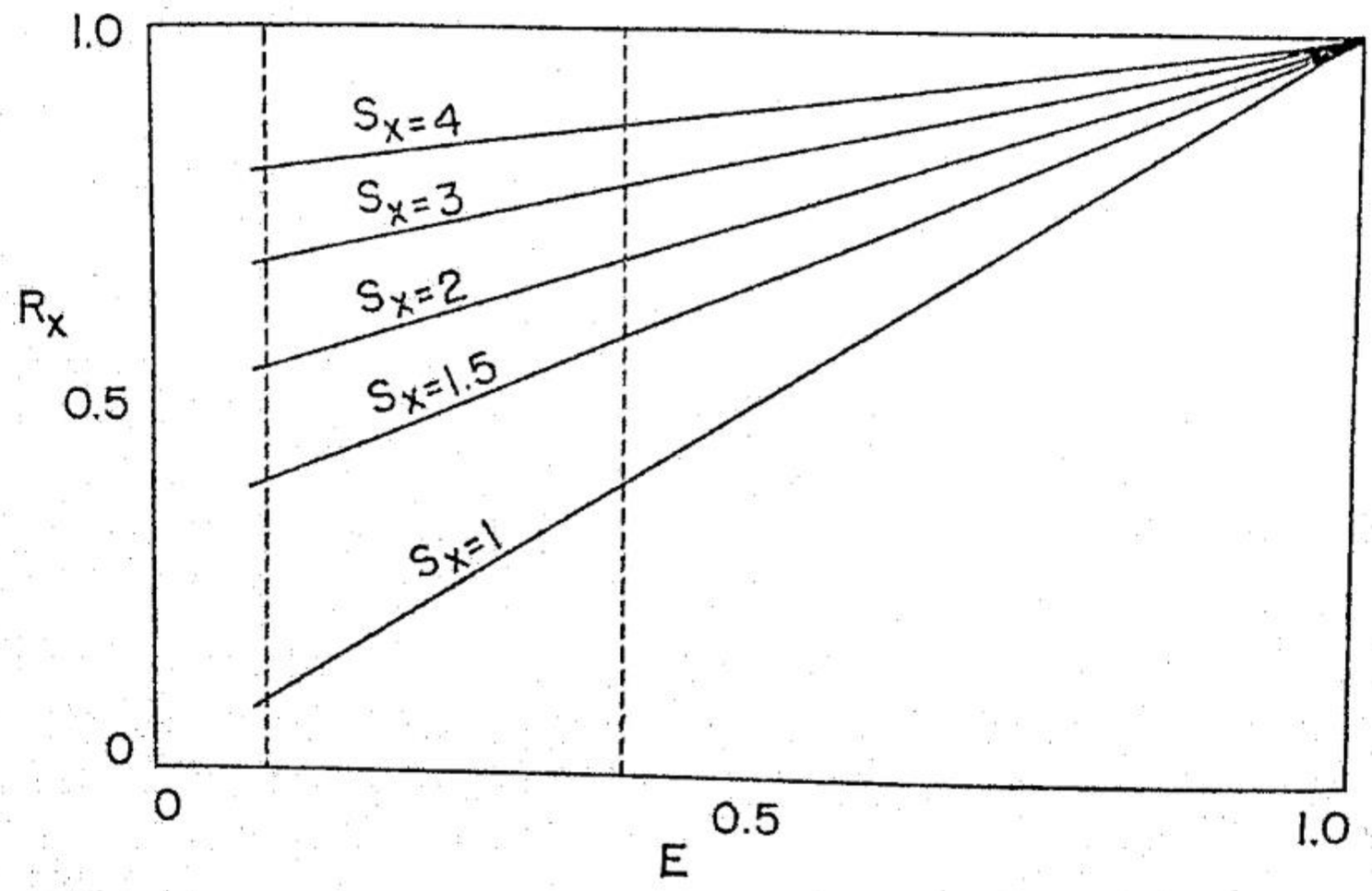
We immediately see a requirement for improved filter media, namely, more accessible surfaces, with affinity for the toxicologically interesting components of tobacco smoke.

In a more detailed discussion, the author has introduced a dimensionless number to characterize a filter's ability to selectively remove a component, or set of components, from mainstream smoke. This selectivity number S_x is defined as the ratio of the concentration of the component x of interest in an "equivalent" unfiltered cigarette to the concentration of the component of interest in the mainstream smoke yield from the filtered cigarette. If $S_x \geqq 1$, selective filtration exists; if $S_x < 1$, other components are exhibiting concentration changes relative to the overall smoke yields for the two cigarettes—the control and the filtered item—the greater S_x, the greater selectivity exhibited.



TEXT-FIGURE 4.—Plot of equation 1 for values of S_x, R_x, and E.

Selectivity is related to the overall efficiency of the filter E and the efficiency with which the component of interest is reduced by the filter R_x. This symmetrical relation is:

$$S_x = \left[\frac{1-E}{1-R_x}\right] \qquad [2]$$

Since taste requires a certain relatively low overall range of E values for practical cigarettes, a plot of equation [1] for values of S_x, R_x, and E is of interest. This is shown in text-figure 4.

This plot clearly shows that, for filters with efficiency between 10 and 40% particulate smoke removal, selectivity values greater than 4 represent about 90% removal of the compound in question. Lower values of S_x represent less reduction, unless we are dealing with a very highly efficient filter.

The selectivity value is useful in following changes in the design of a filter tip. We shall now discuss three aspects of practical filter design in these terms.

Filters made from textile fiber tow are not sufficiently firm, without further treatment, to function properly during normal human smoking. Accordingly, a bonding agent is introduced during filter manufacture whose function is to "weld" together in many places small groups of fibers to form a stiff junction. The resulting mass of fibers is then firm, at least as firm as a well-compacted commercially manufactured cigarette. As noted above, crimp is introduced into the fibers before filter manufacture. This crimp is substantially important in stiffening the bonded array of fiber in the cigarette filter.

An important factor of the manufacture of filters which effects selectivity involves the amount and type of bonding agent used to produce a firm, compact filter structure. When properly chosen, such agents contribute appreciably to the overall selectivity of the product. In table 1 this is illustrated for two simple bonding agents or plasticizers, as they are called commercially, and for a series of complex plasticizers. The fiber involved is a commercial cellulose acetate filter tow typical of that produced around 1963. It is at once clear that the selectivity of a filter can be increased by approximately a factor of two through the use of plasticizers. Further, the amount required is a function of the nature of the chemistry, or polymeric nature of the bonding agent, or both. The data shown here all refer to the selective removal of phenol. Similar effects have been measured by many of the volatile components of cigarette smoke.

TABLE 1.—Selectivity effect of various plasticizing agents applied to secondary cellulose acetate filters

Plasticizer	Amount (weight % of fiber)	S_{phenol}
Triacetin	0	2.1
	6	2.3
	14	3.1
Triethyl citrate	0	2.0
	10	3.1
	15	4.1
Triacetin—polyether A	6	4.8
Triacetin—polyether B	6	3.7
Triacetin—polyether C	6	3.9
Triacetin—polyether D	6	3.4
Triacetin—polyether E	6	4.3
Triacetin—polyether F	6	3.8
Triacetin—polyether H	19	4.4

The length of the filter tip affects selectivity, all other factors being essentially constant. The longer the filter, the higher the selectivity. This assumes an affinity on the part of the fiber within the filter for some component, or set of mainstream smoke components. This effect of length on S_x is illustrated in table 2. Again, the selectivity is for phenol, and the filter is a relatively low efficiency product typical of that made com-

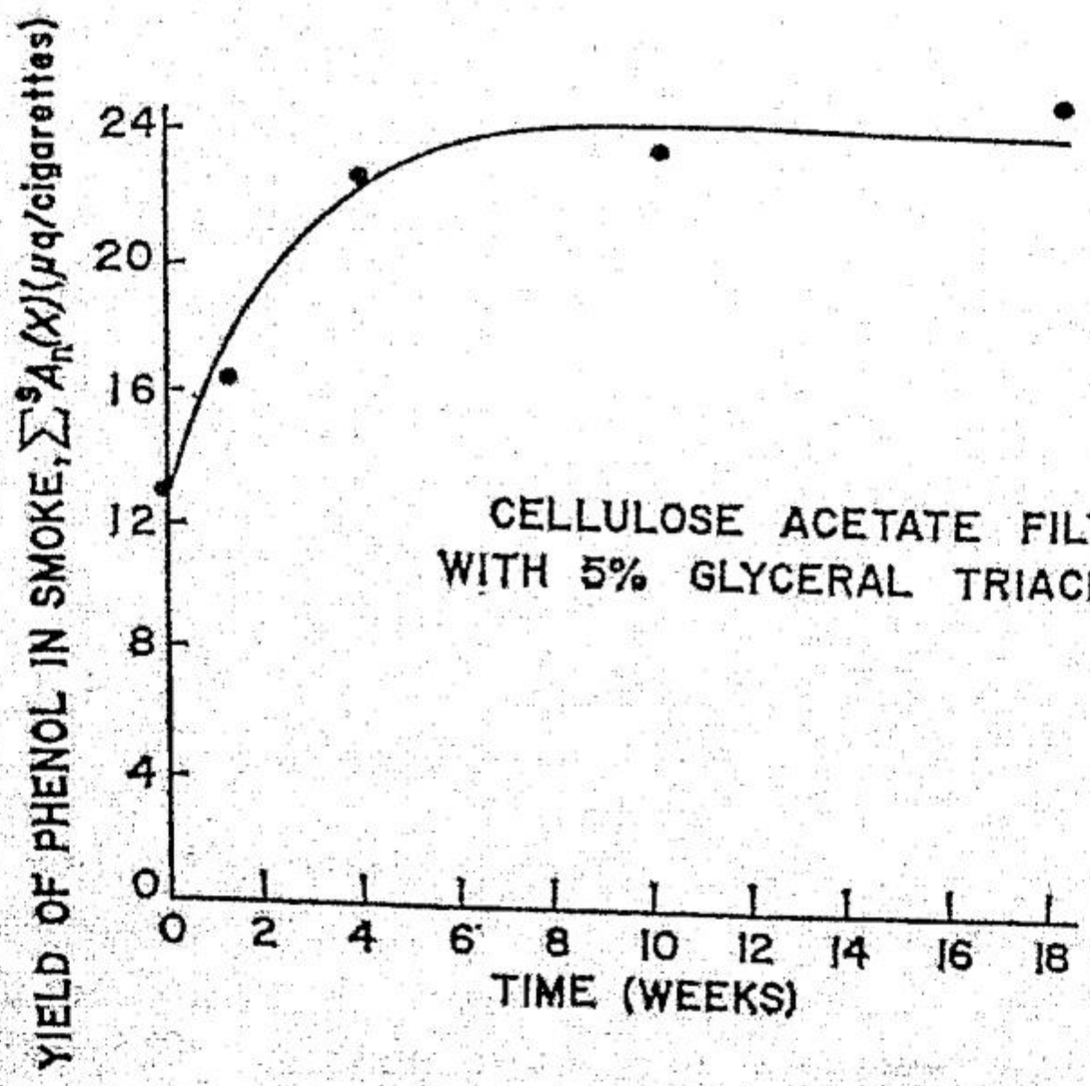
TABLE 2.—Effect of length on S_{phenol} values

Filter length (mm)	Tobacco length (mm)	Total length (mm)	Length smoked (mm)	S_{phenol}
10	68	78	60	2.1
15	68	83	60	2.3
20	68	88	60	2.6
10	75	85	60	1.4
15	70	85	60	2.1
20	65	85	60	2.8

mercially about 5 years ago. The double length of the tip with a fixed total cigarette length effectively doubles the selectivity exhibited by the filter.

Effects of the type shown above are often masked by uncontrolled variables such as the age of the filter and the humidity of the air used obtaining machine-smoked condensate. Text-figure 5 shows the variation in phenol in a smoke as a function of the age of the filter tip. Roughly, twofold increase in phenol yield, and accordingly, a reduction of 50% in selectivity, is discerned readily for the filter in question. This effect is not due to the age of the tobacco or the manner in which the cigarettes are smoked. It is a real consequence of aging within the filter fiber, which in this instance was plasticized or bonded with glyceryl triacetate.

A more complicated effect connected with selective cigarette filters involves compounds in the smoke stream which can be initially sorbed onto the filter and subsequently desorbed into the smoke yield. This is illustrated in table 3 for 3 cigarettes.



TEXT-FIGURE 5.—Variation in phenol in a smoke as a function of the age of the filter tip.

TABLE 3.—Computed $S_{water, n}$

Puff No.	Tobacco*	Cellulose acetate filter	Cellulose filter
1	1.12	0.90	0.74
2	1.26	0.76	0.84
3	1.28	0.78	0.80
4		0.84	0.96
5		0.91	0.97
6		0.97	1.14
7		1.14	1.17
8		1.32	1.99
9		1.09	1.77
All puffs		1.05	1.25

*Obtained from a few puffs on shortened cigarettes.

Column two of table 3 refers to all tobacco in a shorter cigarette than the other 2 cigarettes containing, respectively, a cellulose acetate filter and a crimped paper cellulose filter. The selectivity for the removal of water has been computed from observed data as a function of the puff number. It is seen that the all-tobacco cigarette does selectively filter water to a small extent. Further, this selectivity appears to increase with puff count. The cellulose acetate filter shows an initial reduction in water selectivity, which is then followed by a steady increase in selectivity as more and more of the water initially picked up by the filter and tobacco is released on subsequent puffs. The mean selectivity for water is essentially unity indicating no net overall effect. However, the 100% cellulose filters initially showed quite a low selectivity for water, which increased regularly as the puff count increased. This latter cigarette shows an overall net selectivity that is probably meaningful. The fact that, in the early puff counts the selectivity is less than one, is explainable in the case of the filters because tobacco during these puffs is removing water from the smoke stream. Only water that is present in aerosols reaching the filter can be vaporized as the smoke passes the filter, thus accounting for selectivities that are less than unity.

For typical American blends of tobacco, cellulose acetate filters do not exhibit selectivity in the removal of nicotine. Table 4 gives nicotine selectivity factors for a fairly wide range of filters typical of those produced in 1958. On the average, these selectivity values are extremely close to unity.

When a section containing activated carbon, or a similar absorbent, is added to the fiber filter, many of the more volatile gaseous components of tobacco smoke can be selectively filtered. Table 5 illustrates this situation for both single and dual filters. While very little phenol selectivity is achieved, quite efficient removal of acrolein, hydrogen cyanide, and formaldehyde is achieved.

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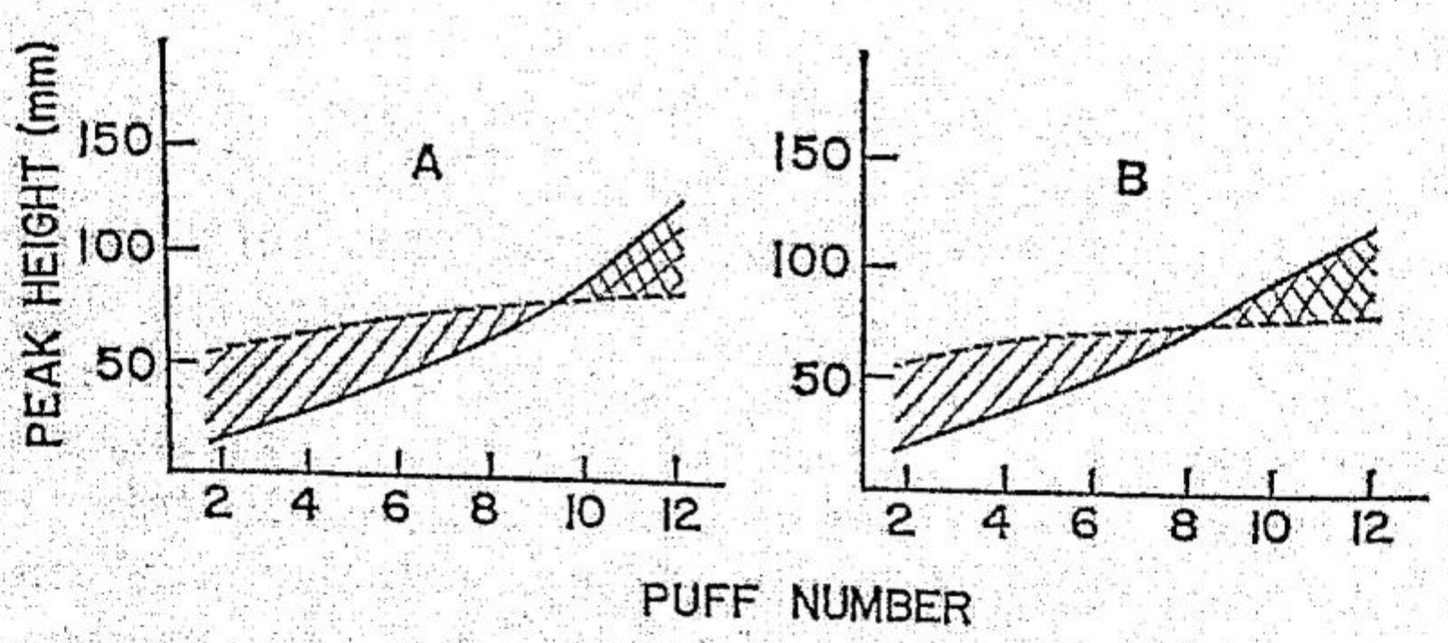
TABLE 4.—Selectivity factors for nicotine (total alkaloids)

Cigarette sample No.	Nicotine based on condensate data	Nicotine based on "tar" data
1	0.91	1.02
2	0.92	0.87
3	0.91	0.99
4	0.97	0.99
5	0.97	1.01
6	1.02	1.03
A	0.90	0.96
B	1.10	1.05
C	0.93	1.01
D	0.99	0.96
E	0.95	0.94
Average	0.97	0.98

TABLE 5.—Computed S_x for single and dual filters

Filter	Volatile phenols	Acrolein	Hydrogen cyanide	Formaldehyde
Single filter (15 mm)				
Viscose	1.1	0.8	0.8	0.8
Secondary acetate	1.9	0.8	0.9	0.8
Paper	1.0	0.7	0.7	0.8
Paper, carbon	1.1	1.6	2.0	1.6
Acetate, carbon	1.3	2.2	2.8	2.2
Bonded, carbon	1.0	10.6	6.5	4.5
Dual filters (7.5–7.5 mm)				
Acetate—paper, carbon	1.5	1.0	1.1	1.5
Paper—paper, carbon	1.1	0.9	0.9	1.4
Acetate—bonded, carbon	1.1	5.3	3.6	3.6
Acetate—acetate, carbon	2.3	1.3	1.3	1.6
Viscose—bonded, carbon	1.0	6.5	3.1	3.0

The active sites in carbon-containing filters can be manipulated to further effect the selective reduction of gas phase components of the smoke exhibiting considerable toxicity to ciliary activity. Among the components that have been reduced are hydrogen cyanide, hydrogen sulfide, ammonia, methyl isocyanate, acetaldehyde, and acetone. Many of these, though strongly sorbed initially on activated charcoal, are often released during later puffs. Text-figure 6 shows two examples of this for acetaldehyde.



TEXT-FIGURE 6.—*Dashed curve* represents yield from unfiltered control cigarette. *Solid line* represents carbon-containing cigarette filter.

The above sections attempt to give a general view of the subject of selective filtration of mainstream tobacco smoke. A filter technology has been developed to measure characteristics of selective filtration. Evidence for selective filtration has been clearly demonstrated in a number of volatile and semivolatile components found in tobacco smoke. It has been shown that selectivity varies with puff number in both gaseous phase and semivolatile substances for which media exist exhibiting selectivity. This complicates somewhat the discussion of the future of selective filtration. Ideally, one would want a filter that increases in selectivity with puff count; some evidence for such has been presented regarding water. However, for the more volatile compounds there is evidence that the puff-by-puff selectivity diminishes with increasing puffs. Clearly, much more empirical investigation needs to be undertaken to find filter media exhibiting a high level of selectivity independent of the puff count.

The work called for above should in no way be construed as an argument against the practice of selective filtration of tobacco smoke or not seeking new means for effecting the efficient removal of mainstream components of smoke. There are many of these; most of them possess tissue-irritating potentials.

It is true that cigarettes fitted with reasonably good selective filters for gaseous components of the smoke stream often yield a bland smoke to the user. Many smokers find this taste relatively undesirable. In the search for safer cigarettes through selective filtration, this widely observed taste difference could be used to promote the use of selectively filtered cigarettes. Clearly, significant public acceptance of such cigarettes does develop in an open marketplace. The writer believes there is no reason why further control of cigarettes should not be aimed in this direction.

Phenol selectivity is generally higher for a given filter than the selectivity for higher phenols such as the cresols. Since smoke fractions rich in phenol and associated compounds have been observed to act as promoters in small animal laboratory studies, it is probably desirable to develop studies showing the phenol selectivity level required to produce either none or a minimum measurable promotion effect in such studies. Such information tempts one to suggest that phenol selectivity might well represent a practical indicator for filter quality.

Similar controlled experiments for the gaseous phase irritants seeking tissue evidence for reduced irritation in the selectively filtered smoke stream apparently are in order. One could anticipate ultimately speaking of filter quality in terms of a set of selectivity values. The components of this set would refer to molecular species or types within the smoke stream which reflect in one way or another the overall reduction in the biological activities of broader fractions of the activity of cigarette smoke.

The above suggestions are given with some hesitation because of the complexity of the chemical and physical composition of tobacco smoke and the significance of these complexities to the broad problem of smoke toxicology.

TOWARD A LESS HARMFUL CIGARETTE

There is, however, one fairly strong observation—the trend to increased selectivity for phenol and other weakly acidic components with longer filter sections is quite real and it is not difficult to achieve a value exceeding 3.5–4.5 for phenol as an indicator. This component of smoke is clearly a promoter in animal studies. There is a real trend toward longer cigarettes on the market. It seems desirable to consider coupling this trend with filters designed to achieve as high a selectivity for phenol and the higher phenols as possible. It seems likely that such a cigarette would yield a smoke of reduced biological activity, at least as judged by animal experiments. One could obviously further aid such a result with a high proportion of low-phenol-yielding tobacco and reconstituted tobacco insofar as this would permit an economic manufacture and customer acceptance.

Comments on Selective Cigarette-Smoke Filtration[1]

DONALD TIGGELBECK, *Manager, Tobacco Industry Sales, Pittsburgh Activated Carbon Company, Pittsburgh, Pennsylvania 15230*

THIS paper outlines some of the aspects governing vapor-phase filtration selectivity. In response to the growing interest in filtration, the Pittsburgh Activated Carbon Company maintains a continuing research program touching on all aspects of the use of charcoal in cigarette filters. One of the more important areas of this research is selective filtration. It is thus necessary to describe our own work and that resulting from cooperative studies with the tobacco industry and other agencies; however, the functions attributed to activated charcoal (activated carbon) are representative of any of several quality types available. To this extent this discussion should be taken generically.

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[1] GLOSSARY OF TERMS USED

Activated Charcoal (Activated Carbon)—An adsorbent derived from a carbonaceous raw material, owing its adsorption capabilities to high internal surface area resulting from its being permeated with pores.

Activation—A process creating pores in a solid so as to improve its adsorptive properties.

Adsorption—A surface phenomenon exemplified by the condensation of a gas on the surfaces of a porous solid.

Adsorption Competition—The tendency for different substances to attempt occupation of the same portion of adsorbent surface.

Angstrom—A unit of length, 10^{-8} cm.

Average Pore—*See* "Pore Structure."

Base Material—Raw material.

Breakthrough Rate—The rate at which a substance being adsorbed approaches influent concentration after breaking through an adsorbent bed.

Equilibrium Capacity—The maximum material which can be adsorbed at system conditions by a unit weight or unit volume of adsorbent.

Impregnant—A material deposited on the surface of an adsorbent to add or enhance a particular characteristic.

Pore—Submicroscopic openings into the structural matter of an adsorbent. In activated charcoals, pores may be of many sizes and shapes, although they are most easily visualized as being cone-shaped.

Pore Structure—1) A curve showing cumulative surface area (or pore volume) plotted as a function of pore diameter. 2) Pores in an adsorbent.

Saturation Capacity—*See* "Equilibrium Capacity."

Surface Area—The total surface presented by an adsorbent. In activated charcoals, normally 99+% of the total surface area is donated by the walls of the pores and is sometimes called "internal surface area."

Virgin Adsorbent (Virgin Charcoal)—1) A charcoal with its surface free of adsorbates. 2) A nonimpregnated charcoal.

Volume Activity—The surface area, pore volume, or similar measure of activity which can be placed in a given adsorber volume. Obtained by multiplying a weight-basis activity measurement by the apparent density.

PROBLEM OUTLINE

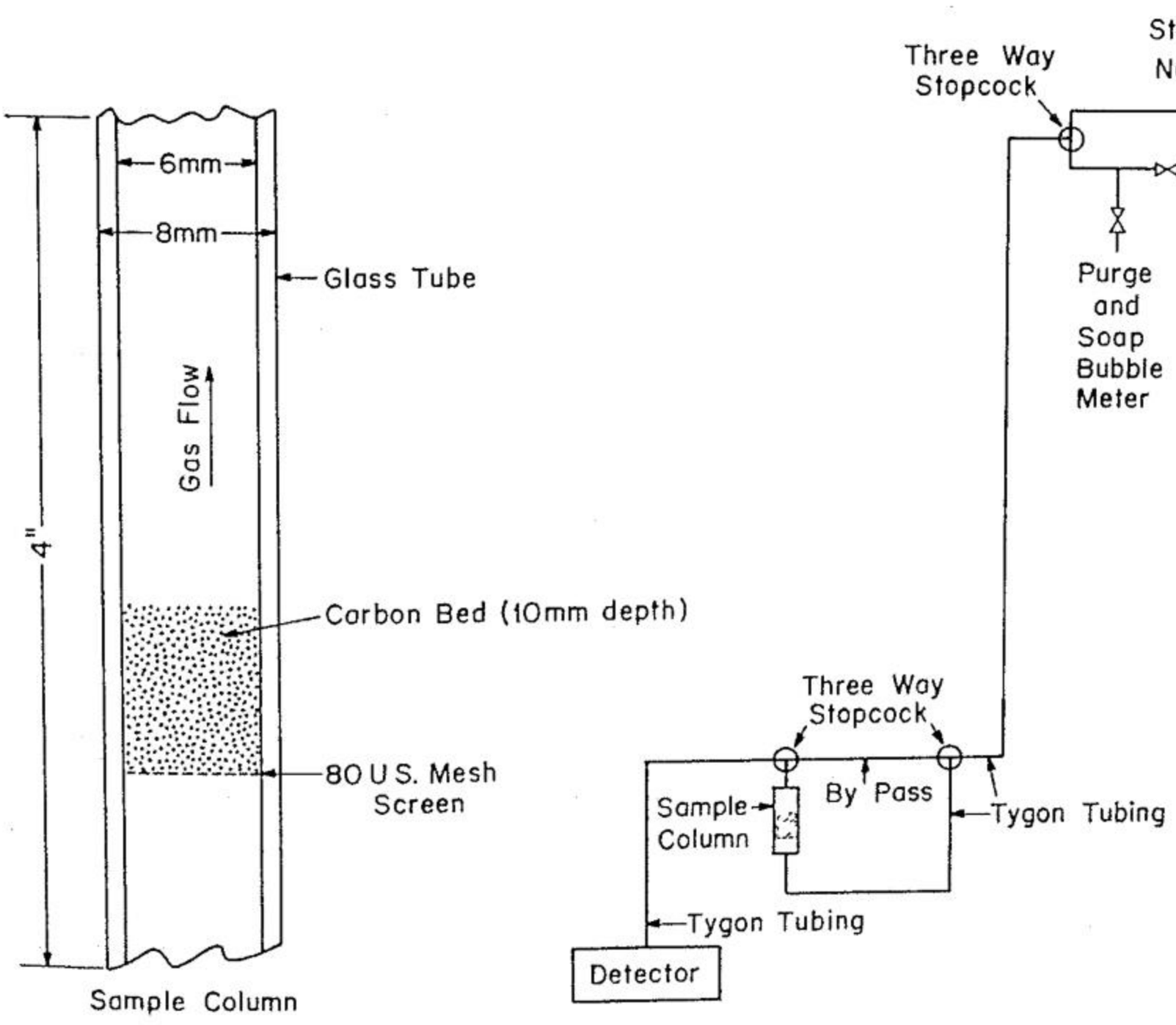
Activated charcoal's performance in stripping most of the compounds in the vapor phase of smoke has been reported by numerous investigators (*1–3*). Other work describes changes observed in biological systems, principally related to improved mucociliary and alveolar macrophage clearance mechanisms resulting from this filtration (*4–7*).

Differences in filter design, amount of charcoal used, and the nature of the charcoal will produce demonstrable changes in filtration efficiency. Part of the work reported to date deals with charcoals that are selective for the general gas-phase components, but are not particularly selective for individual components. That is, various levels of filtration are accomplished, but ratios of compounds removed do not indicate substantial intercompound selectivity. Although a great deal remains to be learned about smoke chemistry and biological effects in particular, it seems logical to assume that certain individual components may eventually merit closer attention from the filtration standpoint. Reasons for this attention could be several including: that a compound occurs in relatively high concentration, that it is found to have greater biological significance, or that it is not as efficiently removed as many other components. These factors have governed our present choice of goals for selectivity studies. Before proceeding, we should define that our use of the word "selectivity" is meant in the context adopted by CORESTA (*8*): A filter component is considered selective if it removes more of a particular material than its control counterpart, as measured against a known and constant standard. Thus a selective charcoal will have enhanced adsorption capacity for a particular compound, but not to the complete exclusion of other compounds.

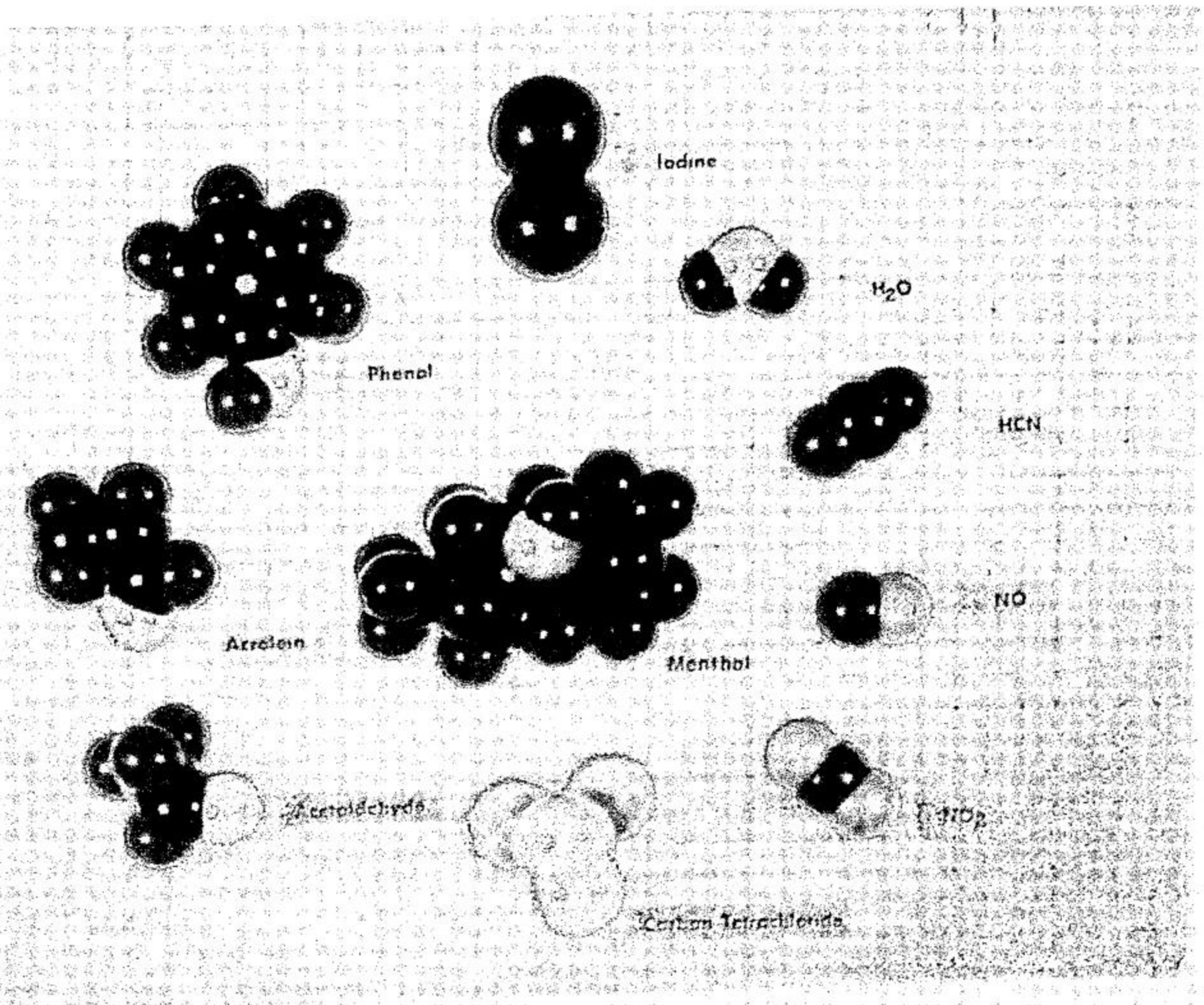
TECHNIQUE

When one considers adding selectivity for a component, or a discrete group of components, two approaches immediately come to mind. The first is to change the charcoal structurally, since it is known that the average structure of the millions of submicroscopic pores permeating the charcoal influences its adsorption capacity for given materials. The second approach utilizes the extensive surface area offered by the charcoal, currently exceeding 1000 ft.^{2}/filter in some commercial cigarettes, to disperse reagents having chemical or physical affinity for the compound of interest. To determine the effectiveness of these approaches, binary mixtures of the target compound carried in a nitrogen stream are initially used (*9*), as illustrated by the data presented (text-fig. 1). Subsequently, promising materials are tested by automatic cigarette smoking. All the charcoals discussed maintain their selectivity during cigarette smoking.

Before we explore the removal of various components, it is interesting to view them as molecular models. Text-figure 2 shows several cigarette-



TEXT-FIGURE 1.--Sample system.



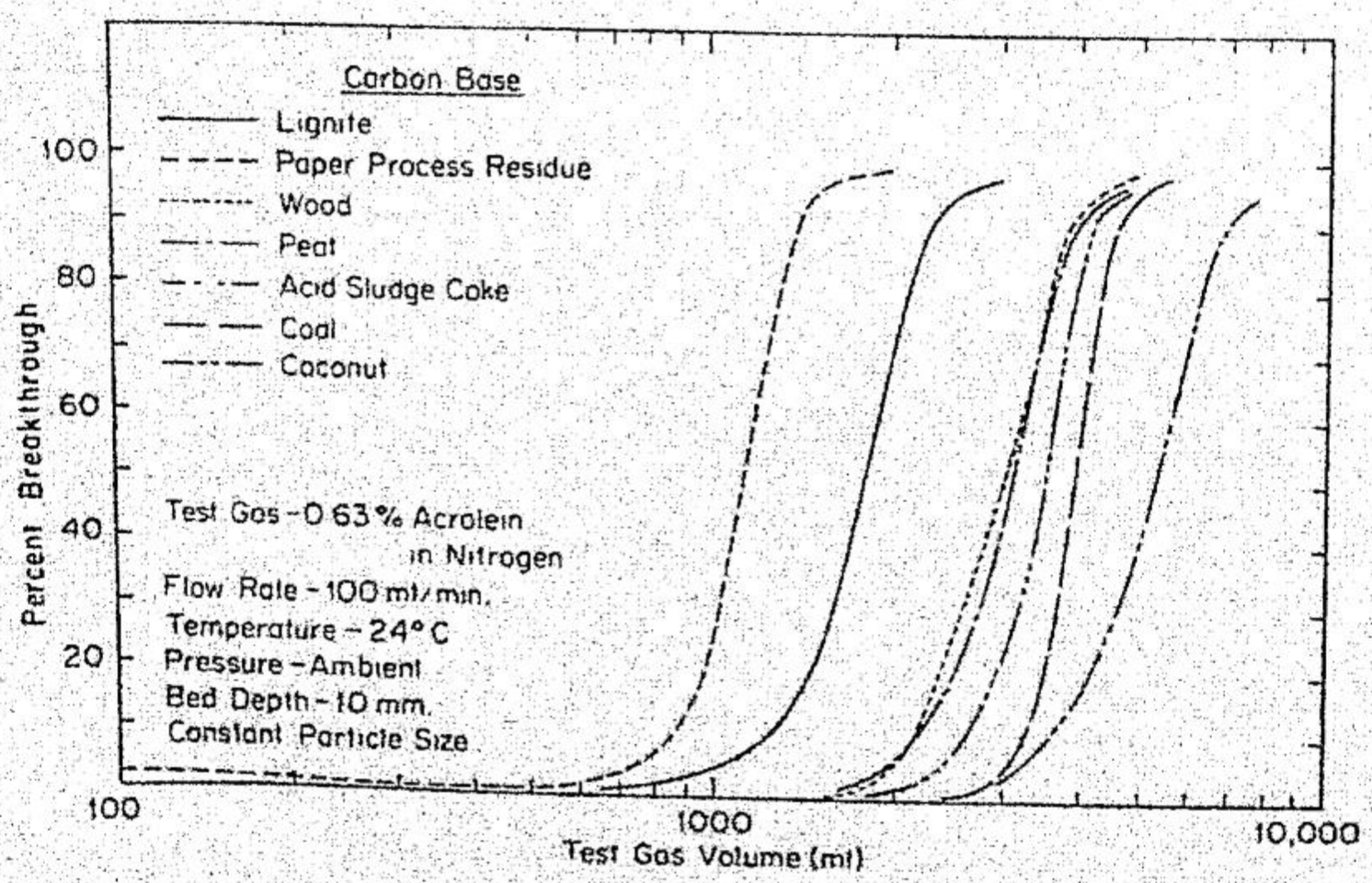
TEXT-FIGURE 2.--Molecular models of various components.

smoke component models. Models of iodine, carbon tetrachloride, and water are also shown, since these are used in various tests to quantify the characteristics of the base charcoal. Each of the squares in the crosshatched background are 1 cm on an edge. The models are constructed so that measuring the number of centimeters gives the dimensions of the molecule in Angstrom units. It is immediately evident that very small differences in molecular size separate one component from the next. Nevertheless, it is possible to activate charcoals that will show substantial differences in equilibrium adsorption capacity for these materials.

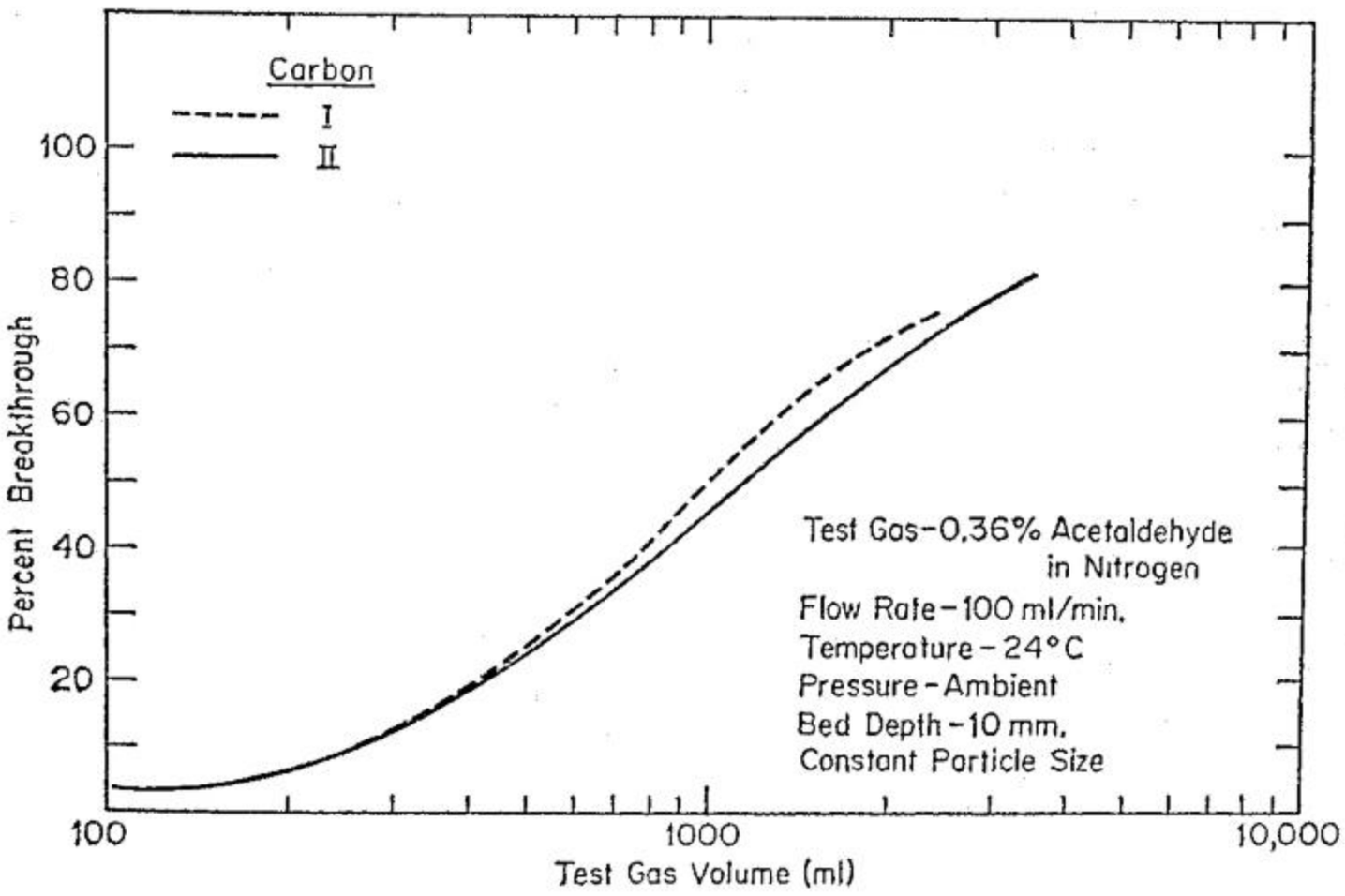
STRUCTURAL CHANGES

The effects of various pore structures on the dynamic and equilibrium adsorption capacities for acrolein are shown in text-figure 3. Each of the raw materials listed yields a characteristic average pore structure when activated under similar conditions. Generally, the charcoals allowing acrolein (*10–13*) to break through soonest have wider pores than the preferred materials, the latter having major percentages of surface area in pores of 15–25 A diameter. Integrating the area to the left of each breakthrough curve shows that the charcoals retarding breakthrough longest also have the highest equilibrium capacities in these cases.

If one followed the implications of these data, he might assume that a charcoal with essentially all its surface area in the preferred pore diameters would be extremely efficient. To test this hypothesis, it is possible to create charcoals with varying surface areas but equal pore structures. An illustration is given in text-figure 4, a breakthrough curve for acetaldehyde. By various equilibrium measurements, including equilibration with acetaldehyde vapor, Carbon II was shown to have twice the equilibrium capacity, twice the total surface area, and an essentially equal pore struc-



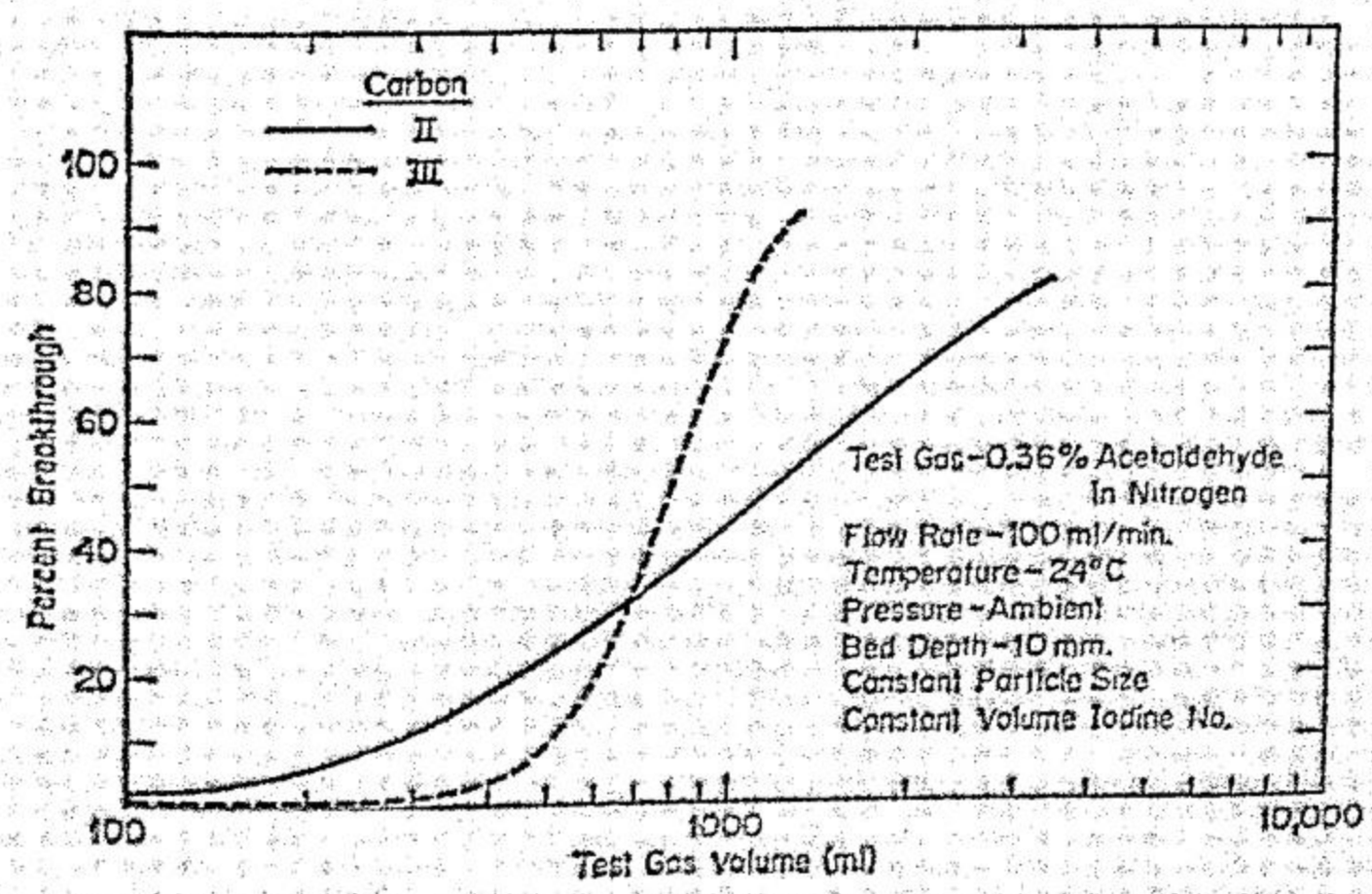
TEXT–FIGURE 3.—Various base materials.



TEXT-FIGURE 4.—Activity differentials in equivalent pore structures.

ture of the preferred type, compared to Carbon I. However, text-figure 4 shows that in a dynamic situation the carbons perform equally. Both allow acetaldehyde to break through relatively rapidly and would be of marginal utility in a cigarette filter. For example, when the same two carbons are used in a cigarette filter, the competition for the charcoal's surface provided by other gas-phase compounds causes an immediate acetaldehyde breakthrough.

Based on an average of current filter dimensions, the charcoal-containing segment has on the order of 1/100 of a second to act. This suggests that the performances of Carbons I and II are limited by the rate of adsorption, which in turn is limited by the ability of the smoke to permeate the charcoal. Therefore, providing extra surface area *per se*, even in pores of the preferred diameter, will not improve selectivity unless wider entry pores are provided. These entry pores allow the smoke to reach internal pores most operative for removing the compound of interest. Text-figure 5 shows the improvement obtained when wider entry pores are added.



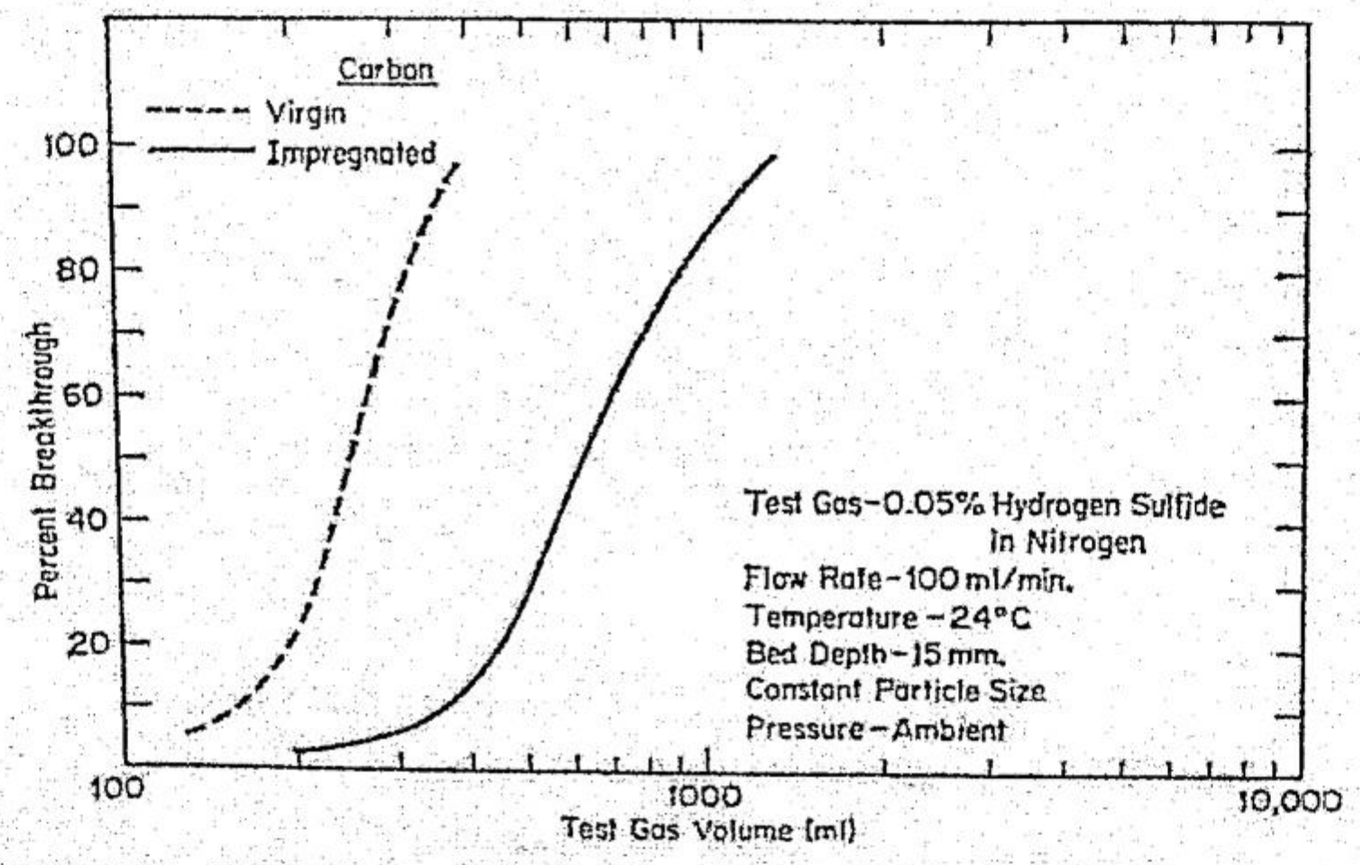
TEXT-FIGURE 5.—Effect of entry pores.

Carbon III, with no increase in total surface area over Carbon II, but with entry pores, is far superior in preventing breakthrough (log axis).

The pore structure represented by Carbon III is typical of that found to a greater extent in current high-quality vapor-phase charcoals. These charcoals are also designed to offer the maximum usable surface area in the minimum volume, so that pore structure changes alone are limited in providing further selectivity progress. This limitation introduces the second approach to selectivity, incorporation of reactive materials.

IMPREGNATED CHARCOALS

It is possible to distribute substances across the surface of activated charcoal, the impregnated substances normally taking the form of thin film or a dispersion of submicroscopic crystallites. This distribution naturally increases the available surface area of the impregnant, at times by factors of several hundred. Since some of the compounds of greatest interest in cigarette smoke are also among the most reactive, the impregnation technique is quite interesting as a practical way to increase selectivity within the physical constraints of a filter. Text-figure 6 shows the effect of an impregnant added to increase selectivity for acid gases such as hydrogen sulfide or hydrogen cyanide. Again, the improved selectivity is demonstrable during cigarette smoking. For instance, if we consider a charcoal loading of 100 mg as representing some of today's commercially available filters, the virgin or unimpregnated control charcoal will remove approximately 65% of the total hydrogen cyanide, while the treated form removes approximately 90%. This improvement in hydrogen cyanide selectivity is obtained with less than 15% reduction in the charcoal's physical adsorption efficiency for other gas-phase compounds. The resultant filter design flexibility affords various delivery ratios for hydrogen cyanide and total gas phase.



TEXT-FIGURE 6.—Impregnant for hydrogen sulfide: Hydrogen sulfide efficiency.

At lower charcoal loadings, when the virgin charcoal is removing less than half the total hydrogen cyanide, the relative improvement offered by the impregnated material is even more striking. A more complete discussion of charcoals of this type is to be presented by our research group at the 21st Tobacco Chemists' Research Conference in Durham, North Carolina.

By techniques similar to those discussed above, we have previously demonstrated charcoals with similar selectivity for acetaldehyde (*9*) and are currently studying selectivity for acrolein and other materials.

The foregoing covers one selectivity goal outlined earlier, the enhanced removal of materials that are also removed by virgin-activated carbons. Of course, there are a few compounds for which the adsorption competition in cigarette smoke is too great—these are essentially not removed by virgin-activated charcoal in filters of practical size. Most of these compounds are nitrogen, unconsumed oxygen, and inert gases. As far as we know, the ones of immediate filtration interest are nitric oxide and carbon monoxide. We are working with both these materials and are attempting to optimize some initially promising results for nitric oxide (*9*, *14*, *15*).

Carbon monoxide, on the other hand, has thus far been very elusive. A scan of available literature on materials reactive for carbon monoxide, other than very powerful oxidants that are nonselective and radically alter the configuration of the smoke chromatogram, shows they fall into one or more groups: 1) materials rendered inactive or "poisoned" by moisture, 2) materials functioning only at high temperature and/or high pressure, 3) materials that are relatively slow acting, and 4) materials carrying a substantial molecular bulk along with a relatively minor reward in reactivity. Taking these general guidelines and comparing them with the: 1a) high humidity, 2a) low temperature and pressure, 3a) very brief contact time, and 4a) size limitations found in cigarette filtration, one can readily recognize that carbon monoxide represents a great challenge to filtration technology.

PARTICULATE PHASE SELECTIVITY

A final selectivity item does not fall strictly under either of the previous headings, but is of interest. For convenience, chemical and biological experiments with cigarette smoke speak in terms of whole smoke, particulate phase, and vapor or gas phase. Particulate phase is usually defined as material retained on the Cambridge filter pad, while vapor phase is material passing this pad. Present cigarette filters employ impaction media such as cellulose acetate or paper to reduce particulate delivery and adsorption with activated charcoal to reduce the vaporous material.

For many considerations, it is important to remember that smoke is actually a continuum, with high-boiling components associated generally,

but not exclusively, with the particulate phase. Low-boiling materials are similiarly found basically but not exclusively in the vapor phase. Intermediate boiling compounds, as anticipated, have substantial percentages in equilibrium with both phases. If the overall smoke equilibrium is disturbed, it naturally adjusts to a new value for each component involved. Fortunately, cigarette smoke's intimate mixture of gases and billions of $\frac{1}{8}$–$\frac{1}{2}$ μ diameter particles allows this spontaneous adjustment to occur within the filter residence time.

Fibers of impaction filters may exert selective solubility or affinity for certain smoke components, or may be treated to add or enhance this selectivity. Probably the best example is found in phenol filtration, which has been described on chemical and biological bases (*16–19*). As he introduced the selective filtration portion of our agenda in this workshop, T. W. George (*20*) referred to other experimental examples presented at the last CORESTA meeting (*8*).

Charcoal filters exert a general selectivity on the particulate phase, even though they are rarely designed to enhance impaction. The mechanism functions through the described imbalance of equilibrium, in some cases readily enough to deliver less of a component than could be predicted from initial examination of the equilibrium distribution or from the overall particulate and gas-phase filtration accomplished. As one would expect, well over 100 compounds are involved to varying degrees and much research remains. Several investigators have expressed interest in the biological aspects of these phenomena (*21–23*). At this time it is difficult to say whether structural or chemical modifications in activated charcoals will yield the greater additional progress.

DESIGN CONSIDERATIONS

T. W. George (*20*) also presented data showing the desorption that occurred in some experimental charcoal filters on the ninth and tenth puffs. Compared to the standard 8-puff analysis, at the rate of one per minute, the latter puffs could show this phenomenon for several reasons. First, smoking a standard king-size cigarette to 10 puffs probably means that the fire cone approaches the filter material and thus increases the filter temperature. The increased temperature creates new equilibrium conditions under which charcoal and other filter substances desorb some material originally retained at a lower temperature. The second possibility could relate to the pore structure of the charcoal used, in that charcoals with pores wider than necessary do not retard smoke components satisfactorily, as illustrated in text-figure 3. The third possibility relates to the amount of charcoal used, since less than an optimal amount could have been spent on the first few puffs. Of course, any combination of these factors could also be involved. Design routes to a solution of this problem could therefore include keeping the temperature of the charcoal lower by

insertion of a cellulose or paper buffer or by extension of the filter overwrap. Another step could be changing to a charcoal which held the adsorbed material more tenaciously. A third would increase the amount of charcoal used to allow for the increased adsorption load of the last puffs which, as is evident from other data, are comparatively high in their concentration of materials to be removed. Similarly, some combination of these factors will also effect a solution.

CONCLUSION

In this brief presentation, both the potentials and limitations of selective filtration have been illustrated. As smoke chemistry continues to be explored and medical technology continues to be refined, the concept of selectively altering the makeup of smoke should find increasing utility.

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[illegible]FUL CIGARETTE

with the properties described above and that resulting "tars" might no longer cause tumors in the skin of mice.

This report includes 1) studies on tumor growth inhibition by tobacco-smoke condensates and 2) studies on tumor growth inhibition by derivatives of benzo[*rst*]pentaphene.

METHODS

Studies on Inhibition of Tumor Growth in Mice by Cigarette-Smoke Condensate

Cigarette-smoke condensate.—Cigarette-smoke condensates from cigarettes of the 5 leading commercial American brands, smoked in machines under conditions previously described (*8*), were denicotinized by the following procedure.

Smoke condensate dissolved in a 9 : 1 methanol-water solution was passed through a cation exchange resin under nitrogen pressure to remove the basic fraction. After being washed repeatedly with solvent mixture, the effluent was set aside and the bases were eluted from the column into a separate receiver with methanol : 6N ammonia mixture (9 : 1). The solvent was removed from this effluent and the residue dissolved in 9 : 1 methanol-water. Nicotine in a portion was determined by a gravimetric procedure, and silicotungstic acid exactly equivalent to the nicotine in the eluate was added to precipitate this base quantitatively. The nicotine complex was filtered, washed, and discarded. Mother liquor and washings containing bases not precipitated by silicotungstic acid were then returned to the original effluent from the cation exchange resin. This combined solution was then evaporated dry and made up to a 50% acetone solution. Ten ml of this solution was added to 95 ml of Ringer's physiological saline containing 2% of a polyoxyalkylene derivative of sorbitan monolaurate [Tween 20 (a wetting agent)]. The resulting mixture was treated in a VirTis 45 homogenizer at 45,000 rpm for 2 minutes and at lower speed for another 2–4 minutes to reduce foaming. After the mixture was allowed to stand until the foam disappeared, the resulting emulsion was placed in a Büchler FE 1000 flash evaporator for 30 minutes at 30°C for removal of the acetone.

Studies on lung tumors.—Female A/He mice were obtained from The Jackson Laboratory, Bar Harbor, Maine. They were used at the ages indicated in table 1 and received the intravenous cigarette-smoke condensate injections listed in the same table. Control animals received only Ringer's solution containing 2% Tween 20, and an amount of acetone corresponding to that contained in the smoke condensate suspensions.

TABLE 1.—Studies on lung tumors in mice

Expt. No.		Number of animals		Age of animals (wks)		Intravenous tobacco-smoke condensate				Body weight change from start to killing (g)	Tumor incidence % survivors*
		At start	At killing	At start	At killing	mg/injection	Number given injections	Interval (wks)	Total dose (mg)		
1	Treated	36	33	7	31	2	1	—	2	+6.2	3
	Control	36	33	7	31	0	1†	—	0	+5.2	36
	Untreated‡	50	50	7	31	0	0	—	0	—	30(0)
2	Treated	40	32	7	31	3	1	—	3	+5.9	22
	Control	39	30	7	31	0	1†	—	0	+5.5	47
	Untreated‡	50	50	7	31	0	0	—	0	—	30(0)
3	Treated	50	44	20	35	5	7	2	35	+0.9	18
	Control	50	41	20	35	0	7†	2	0	+0.2	41
	Untreated‡	50	50	20	35	0	0	—	0	—	38(15)
4	Treated	20	20	38	46	5	8	1	40	−0.8	10
	Control	20	20	38	46	0	8†	1	0	−0.7	60
	Untreated‡	50	50	38	46	0	0	—	0	—	53(40)
5	Treated	20	17	32	44	10, 15, 20	3	4	45	+1.8	12
	Control	20	15	32	44	0	3†	4	0	+3.7	67
	Untreated‡	50	50	32	44	0	0	—	0	—	53(40)
6	Treated	14♂	14	38	46	5	8	1	40	−0.2	46
	Control	14♂	14	38	46	0	8†	1	0	0	86
	Untreated§							—		—	—§

*Figures in parentheses are percentage of animals with lung tumors in untreated series at age when treatment in experimental animals was begun.
†Ringer's solution with 2% Tween 20.
‡Animals receiving no treatment. This experiment was not done simultaneously (*see* text).
§No data available in ♂♂.

The animals were weighed individually at the start of the experiment and again before being killed. The procedure of counting lung tumors was that developed by Heston (*9*). The animals were killed with ether, the chest was opened, and approximately 0.5 ml of 4% formaldehyde solution was injected into the trachea to distend the lungs. The lungs were then removed and studied under a dissection microscope at 10× magnification, and tumors were then counted on the surfaces of all lobes. In selected cases, sections were made and stained with hematoxylin and eosin solution for histological study.

A systematic study of the lung adenoma incidence in untreated animals was carried out in several hundred young A/HeJ mice. Fifty of these mice were killed at bimonthly intervals, their lung surfaces were studied as indicated above, and a sampling of histological sections was made. This study was not simultaneous with that of the treated animals and their controls who were given Ringer's solution.

To test the effect on lung adenoma formation of inert particulate matter injected intravenously, 29 female A/J mice received, beginning at 1 month of age, 5 intravenous injections at monthly intervals of 0.5 mg of a suspension of Teflon particles in 0.1 of Ringer's solution with 2% Tween 20.

The animals were killed when 7 months of age and the lungs were examined as described above. Control animals received injections of only the vehicle on the same schedule. Twenty-eight mice received injections, on a similar schedule, of denicotinized tobacco tar (0.5 mg in 0.1 ml of the same vehicle).

Studies on subcutaneous sarcomas.—(*a*) *Induced sarcomas:* One hundred and thirty-two male C57BL/6 BIO mice received 0.5 mg of 3,4,9,10-dibenzpyrene (benzo[*rst*]pentaphene) (DBP) in 0.1 ml of peanut oil into the left groin. This is the standard procedure used in the authors' laboratory for the induction of subcutaneous sarcomas (*10*).

Sixty-six of these animals were given intraperitoneal injections of tobacco-smoke condensate. This condensate was dispersed, as described above, at a 5% concentration in Ringer's solution containing 2% Tween. Each animal received 10 mg once a week for 2 weeks, beginning after the carcinogen injections, and subsequently 5 mg twice a week until tumors appeared. The other 66 mice treated with dibenzpyrene served as controls and received only Ringer's solution.

(*b*) *Transplanted sarcomas:* Tumors induced by the subcutaneous injection of 500 μg of DBP and subsequently carried in C57BL/6 BIO mice for 13 generations were implanted into 21 male C57BL/6 BIO mice, 2–3 months old. Ten of the animals received daily intraperitoneal injections of 1 mg of tobacco-smoke condensate in Ringer's solution for 14 days, starting on the day of implantation. The other 11 animals served as controls, receiving only Ringer's solution. The animals were then weighed and killed, and the tumors were weighed.

Studies on Tumor Growth Inhibition by Derivatives of Benzo[*rst*]pentaphene

The derivatives of benzo[*rst*]pentaphene studied were: benzo[*rst*]pentaphene-5,8-diol, diacetate, benzo[*rst*]pentaphene-5,8-diol, dibenzoate, and benzo[*rst*]pentaphene-5,8-dione (DBP-5,8-quinone).

Studies on carcinogenicity of potential inhibitors.—To determine their carcinogenicity, 500 μg of the compounds studied was injected subcutaneously into the groin of C57BL/6 mice, the injection sites were palpated weekly, and the tumors found each week were recorded (percentage of survivors with tumors).

Studies on inhibition of lung tumors.—A/J mice were used in these studies. For a study of tumor inhibition, groups of 20 animals received intravenous injections of 500 μg of the inhibiting compound studied in 0.1 ml Ringer's solution and Tween 20, and 1 month later, 500 μg of DBP was injected intravenously. Three months later, the lungs were examined as described above.

Studies on inhibition of subcutaneous carcinogenesis.—C57BL/6 male mice received 500 μg of the potential inhibitors in 0.1 ml of tricaprylin subcutaneously into the groin. Two weeks later, 500 μg of the carcinogen, DBP, was injected in tricaprylin subcutaneously into the same site. Palpable tumors were recorded, as described above, and transplantation studies and histological examinations were made of some of the tumors that developed.

Studies on inhibition of transplanted tumors.—Trocar transplantations of Sarcoma 180 were made into the groin of C57BL/6 male mice, and beginning 24 hours later intraperitoneal injections of 500 μg of the potential inhibitors in tricaprylin were given daily for 7 days. Control animals received only tricaprylin by a similar injection schedule. On the 10th day after beginning of treatment, the tumors were dissected and weighed.

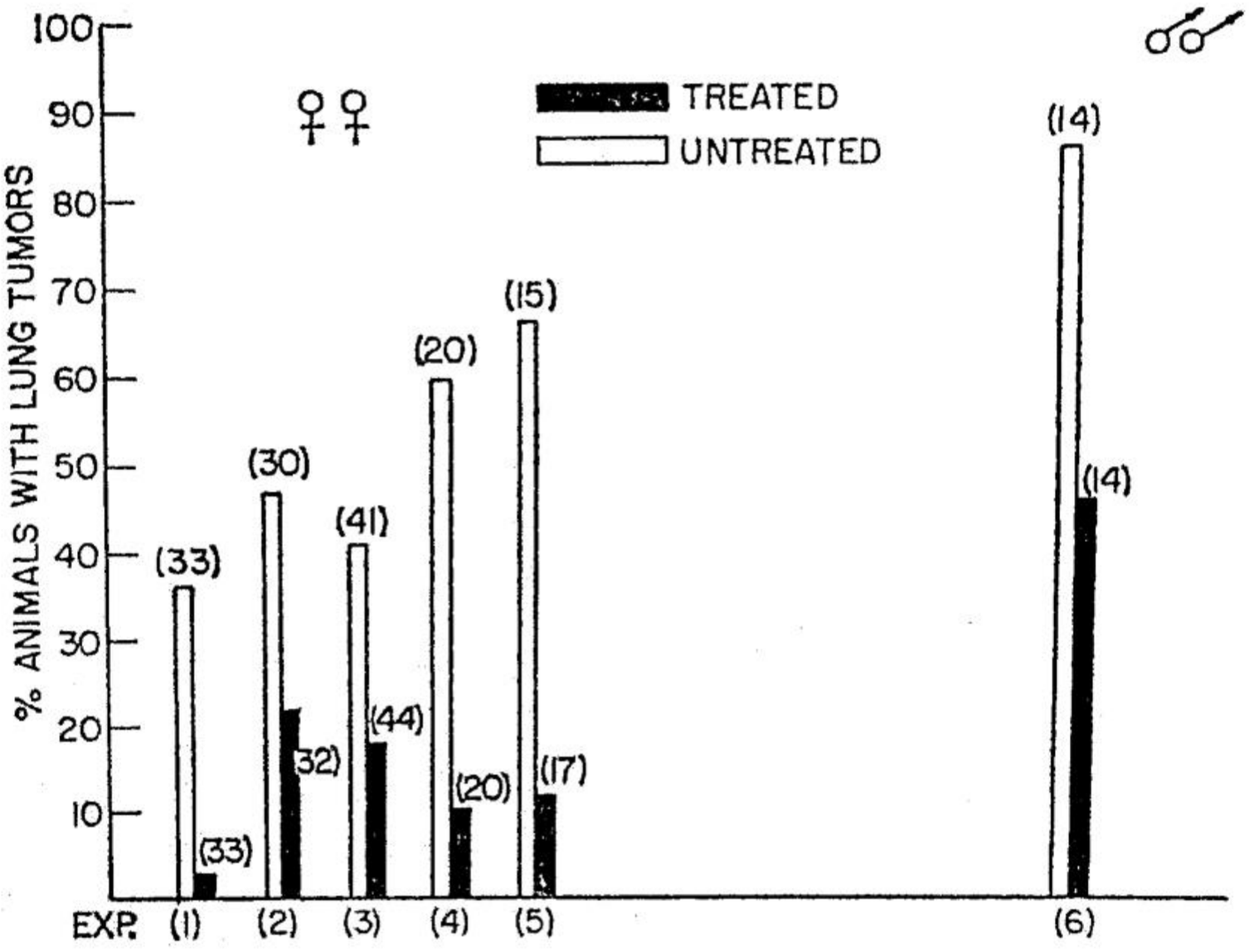
RESULTS

Effects of Tobacco-"Tar" Condensate on Spontaneous Lung Adenomas in A/HeJ Mice

The results are illustrated in text-figure 1.

These data apply to lung adenomas that are discernible under the dissecting microscope at 10× magnification (diameter of 0.2 mm or more). Under these conditions, a reduction of the number of animals with lung tumors takes place in all groups having received tobacco-smoke condensate where the tumor incidence reaches from 1/10–1/2 of that of the controls.

The body weight changes in treated animals were not markedly different from those of the controls.



TEXT-FIGURE 1.—Effect of denicotinized acetone-free tobacco-smoke condensate on the incidence of spontaneous lung tumors in A/HeJ mice. *Numbers in parentheses on top of bars* indicate number of animals in each experiment. *Numbers in parentheses at bottom* of graph identify individual experiments.

Histological examination showed that, even though the dissecting microscope did not reveal any lung tumors, in some cases, microscopic tumors could be seen on histological examination.

By histological examination, as many tumors could be demonstrated in treated animals as had been seen in the controls by means of the dissecting microscope. For clarification of this situation, it will be necessary to do serial histological studies of entire lungs in treated and control animals. It would appear, however, that the intravenous injection of tobacco-smoke condensate arrested the spontaneous lung adenomas of A/HeJ mice at an early stage and inhibited their subsequent growth.

In addition, when older animals were used, fewer animals with tumors were counted after the treatment than would have been expected from a separate, untreated control series to have tumors before treatment began. A regression of already existing tumors following tobacco-smoke condensate application is thus suggested by these observations, although not conclusively established.

Studies with Teflon particles in Ringer's solution injected intravenously have shown that the presence of particulate matter in the pulmonary circulation does not affect the incidence and growth rate of lung tumors. The animals receiving Ringer's solution with Tween had an incidence of lung tumors of 21%; those receiving Teflon, 27.6%; and those receiving denicotinized "tar," 14%.

Effects of Tobacco-Smoke Condensate on Transplanted and Induced Subcutaneous Sarcomas

The growth rate of subcutaneously induced sarcomas is slowed significantly by intraperitoneal injection of tobacco-smoke condensate. However, the number of animals in which sarcomas are eventually produced is not altered.

The growth rate of subcutaneously transplanted sarcomas is inhibited to a statistically significant degree by the intraperitoneal injection of tobacco-smoke condensate (table 2). The body-weight loss in the treated animals is not sufficient to explain this reduced tumor-growth rate.

Effects of Derivatives of DBP

Lung tumors.—The DBP-quinone, when given alone without administration of DBP, reduced the number of countable spontaneous lung tumors in A/J mice. When administered before intravenous injection of DBP, the DBP-quinone reduced the numbers of lung tumors per animal as well as the incidence of animals with lung tumors. Lung tumor inhibition was less marked with 5,8-diol, diacetate, and with 5,8-diol, dibenzoate (text-fig. 2).

Subcutaneous carcinogenesis.—A significant reduction occurred in the carcinogenic potency of subcutaneously injected DBP with each of the three tested derivatives of DBP. This was most marked with DBP-quinone (text-fig. 3).

Inhibition of transplanted tumors.—DBP-quinone caused inhibition of Sarcoma 180 of a degree sufficient to consider this compound as a chemotherapeutic agent. The two other derivatives had effects on transplanted tumors (table 3), which, while statistically significant, are insufficient to attribute chemotherapeutic activity to these compounds.

DISCUSSION

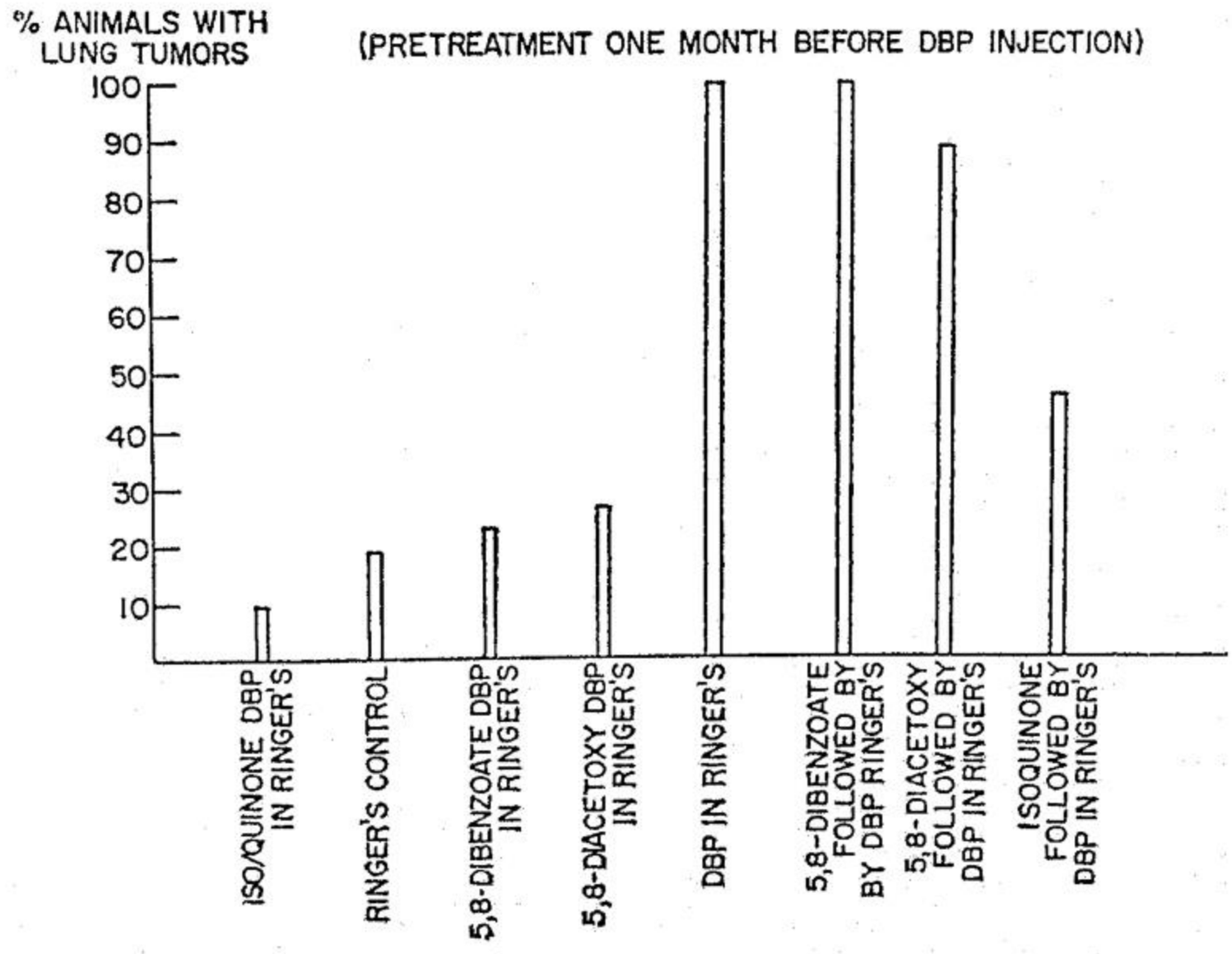
Evidence has been presented that cigarette-smoke condensate contains substances that reduce tumor growth under certain circumstances. There appears to exist in cigarette "tars" an equilibrium between initiators, promoters, and inhibitors of carcinogens with an excess of the initiators and promoters, as measured by mouse-skin painting. The identification and isolation of inhibitors, while possible, would be a difficult and slow operation. More promising is a study designed to search for inhibitors of carcinogenesis and tumor growth among such agents already known and especially among chemicals related to polycyclic hydrocabrons known to occur in "tars."

Inhibitors of carcinogens can be divided into two groups: (*a*) those that stop the progress of a cancer already established and (*b*) those that

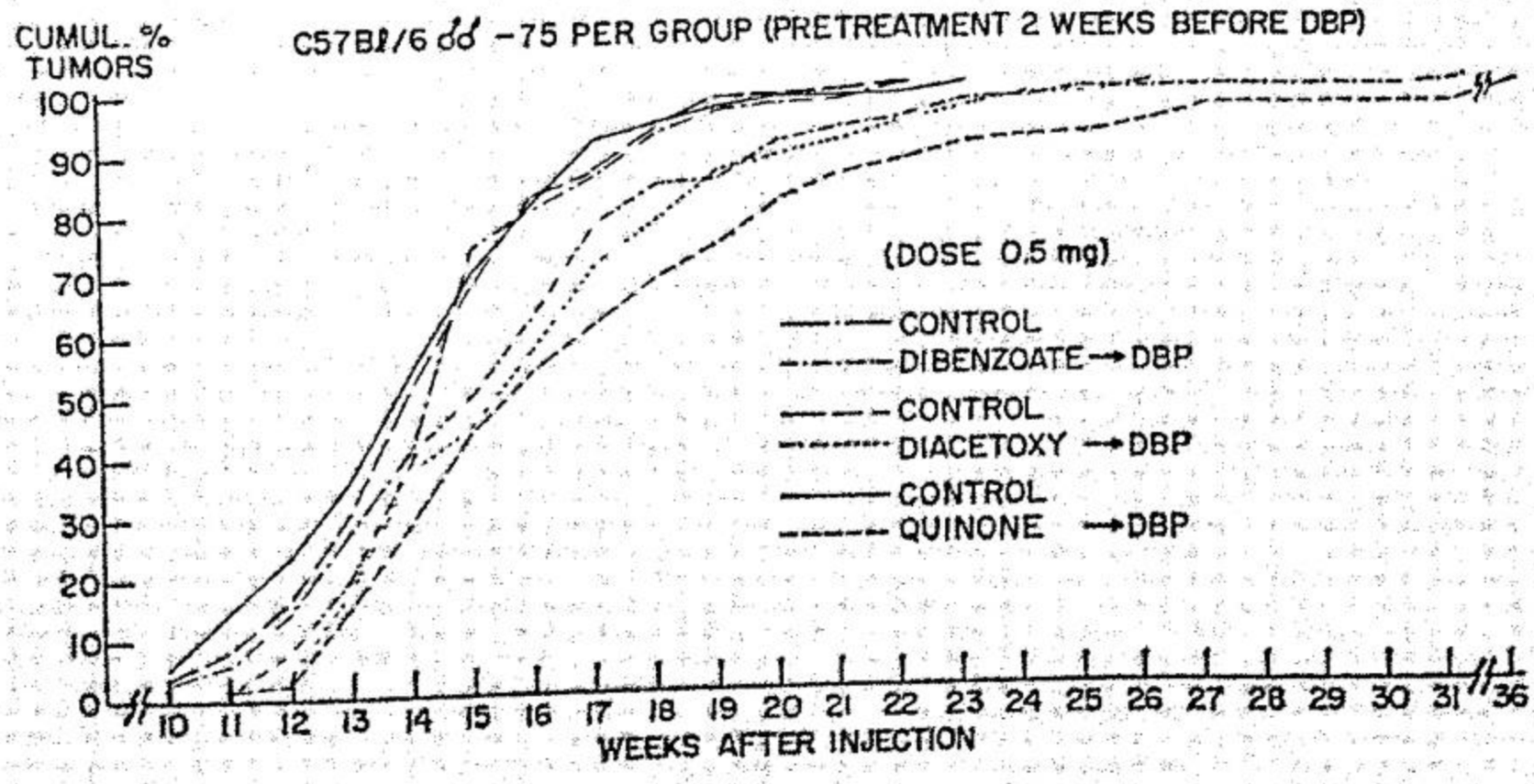
TABLE 2.—Effect of intraperitoneal injections of tobacco-smoke condensate on subcutaneously transplanted DBP-induced sarcomas in C57BL/6 mice

Animals	Number	Average tumor weight (g)	Weight (average at start)	Body weight change (g)	
				Uncorrected	Corrected for tumor
Controls	11	1.3 ± 0.23* (1.0–1.6)†	22.7	+1.0	−0.3
Treated	10	0.9 ± 0.3* (0.5–1.6)†,‡	24.2	−1.2	−2.1

*Standard deviation.
†Range in parentheses.
‡A t value of 3.3 indicates statistical significance of the difference between tumor weights of treated animals and controls (at a 1% probability level).



TEXT-FIGURE 2.—Effect of pretreatment with three dibenzpyrene derivatives on lung tumor induction with dibenzpyrene (intravenous route)—A/J female mice (25–35 per group).



TEXT-FIGURE 3.—Effect of pretreatment with three dibenzpyrene derivatives (iso-dibenzpyrenequinone, 5,8-diacetoxydibenzpyrene, and 5,8-dibenzoate-dibenzpyrene) on subcutaneous tumor induction with dibenzpyrene in peanut oil.

delay or prevent tumor formation (*11*). Among the former group, several quinones have been shown to have carcinostatic activity. These are the 9,10-phenanthrene quinone (*12*) and its precursor, 9,10-phenanthrene hydroquinone-bis-glycyl ester (*13*), and the 2,3,5-tris(ethylenimino)-*p*-benzoquinone (*14*). These quinones undergo a redox cycle in tumor cells; H_2O_2 is formed during the autoxidation of the hydroquinone. The amount of H_2O_2 is especially large in aerobically glycolyzing cells (*13*).

TOWARD A LESS HARMFUL CIGARETTE

TABLE 3.—Chemotherapeutic tests of three derivatives of DBP*

Compound	Tumor	Number of animals		Average tumor weight (g) †		t	P
		Treated	Controls	Treated	Controls		
Di-acetate	Sarcoma 1	10	10	0.7 ± 0.09 (0.7–1.3)	1.0 ± 0.27 (0.7–1.3)	3.3	<0.01
Di-acetate	Sarcoma 180	10	10	0.4 ± 0.1 (0.3–0.6)	0.6 ± 0.26 (0.3–1.0)	2.2	0.025
Quinone	Sarcoma 180	9	10	0.5 ± 0.2 (0.3–0.9)	0.8 ± 0.6 (0.1–2.0)	2.1	~0.025
Di-benzoate	Sarcoma 180	7	10	0.6 ± 0.17 (0.3–0.8)	0.9 ± 0.33 (0.2–1.2)	3.3	0.01

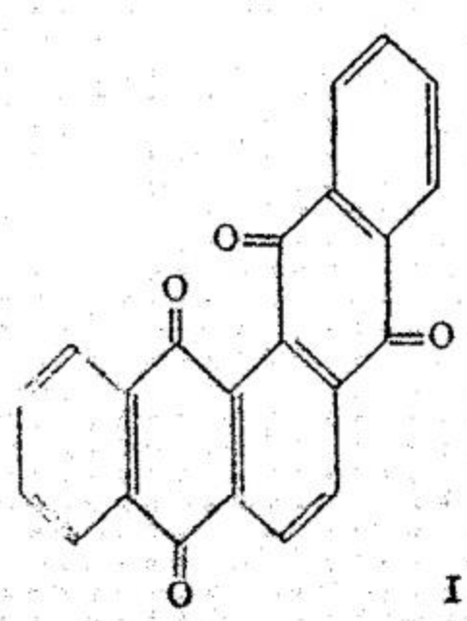
*Promising chemotherapeutic activity is defined as reduction of tumor size in treated animals (as compared to tumors of untreated controls) by more than 33.3%. Thus while all three tested compounds produced statistically significant reduction of tumor size, only the quinone shows chemotherapeutic promise.

†± Standard deviation range in parentheses.

The second group (delay and prevention of tumor formation) consists mainly of compounds structurally related to the carcinogens. These compounds are noncarcinogenic or weakly carcinogenic and presumably act by competition for receptor sites. Partially hydrogenated carcinogenic hydrocarbons, such as dihydro and hexahydro DBA, are inhibitors of the carcinogenesis by the parent compound (*15*), and the carcinogenic power of the same hydrocarbon, DBA, is distinctly reduced by a concomitant application of its aza analog, the 1,2,5,6-dibenzacridine (*11*).

In the case of the DBP-5,8-quinone (benzo[*rst*]pentaphene-5,8-dione) and the 5,8-diol, diacetate (benzo[*rst*]pentaphene-5,8-diol, diacetate) (from which the quinone can be formed enzymatically *in vivo*), the two types of inhibition could be anticipated: competitive inhibition of the DBP activity and carcinostatic effect due to the quinone-hydroquinone system.

The greater effectiveness of the DBP-quinone demonstrated in the present experiments supports this working hypothesis. For these reasons, we are now investigating the following quinones and aza-derivatives of DBP: the pentaphene-5,8-13,14-diquinone (I), obtained from DBP-5,8-quinone by oxidation, the DBP-diaza-5,8-quinone (II) (benzo[*rst*]pentaphene-13,14-diaza-5,8-dione), and the diaza-DBP (III) (benzo[*rst*]pentaphene-13,14-diaza). The latter compound has been tested for carcinogenic activity (*16*); after 14 months, no malignant tumors have developed.



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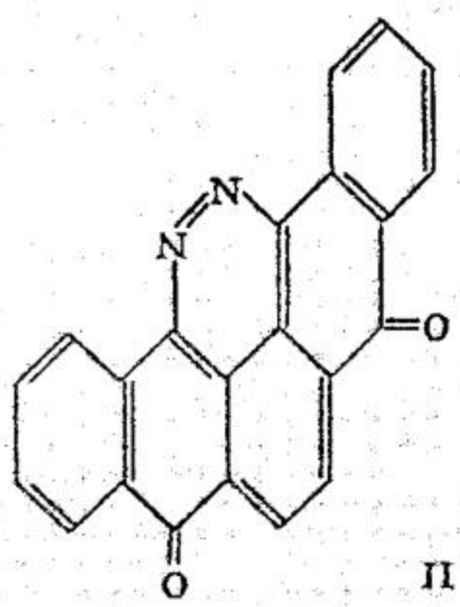

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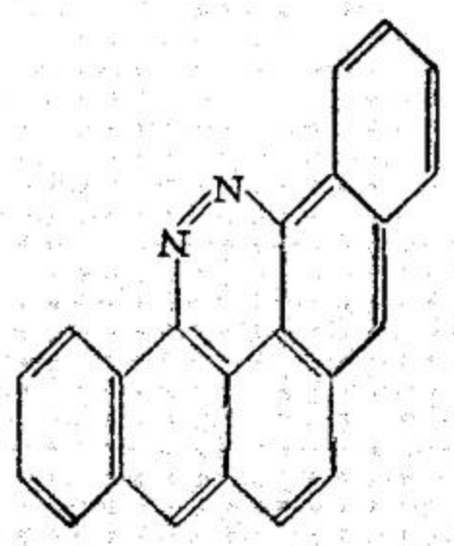

III

The above-mentioned quinones and their derivatives may not have the physical requirements for use as additives in tobacco blends because of their low volatility. It is, therefore, suggested that a series of more volatile compounds which would release the active inhibitors during the smoking process be made and tested.

It must be emphasized that all of our efforts described in this report were directed toward the preparation of cigarettes that will yield "tars" which are noncarcinogenic for mouse skin. We are attempting to achieve this by applying the concept of chemoprophylaxis of carcinogenesis reviewed by Wattenberg (*17*). We are not concerned here with the question of whether this bears any relationship to lung cancer in man. However, since the carcinogenic properties of cigarette-smoke condensate for mouse skin are the only generally measured ones and have been used to bolster the argument that cigarettes may cause cancer, it is logical to postulate

that "tars" that will not cause cancer in mice deserve long-term clinical testing in man. We believe that such "noncarcinogenic tars" will eventually be obtained by increasing their proportional content of anticarcinogens.

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Chapter IV

SUGGESTED MEASURES FOR LESS HARMFUL CIGARETTES

A.—Recommendations by Individuals

B.—Summary of Workshop

RECOMMENDATIONS BY INDIVIDUALS

Since the harmfulness of cigarettes is based on the statistical association of cigarette smoking with emphysema, cardiovascular disease, and lung cancer, proof that a cigarette is less harmful will have to be based on the demonstration that such an association no longer exists. To prove such a negative association will be extremely difficult, particularly inasmuch as a certain incidence of emphysema, cardiovascular disease, and lung cancer exists independent of smoking and may increase in frequency as air pollution continues to rise.

For these reasons, progress in this field will depend on the availability of generally accepted chemical and experimental criteria to establish the safety of smoking devices. Establishment of more or less arbitrary criteria for safety of consumer products by consensus of competent experts has long been an accepted procedure in the regulation of foods, drugs, and cosmetics.

Obviously, formulation of such standards is a step entailing grave consequences and must be done with circumspection and be interpreted with a minimum of assumption and a maximum of factual data and scientific objectivity.

Although a dose-response relationship for nicotine and "tar" exists within the range of their toxic doses, certain experiments, in which nicotine or "tar" was used to produce cardiovascular responses or skin cancer in animals, showed that the absence of these two components from cigarette smoke by no means establishes the absolute safety of a cigarette.

The clinical evidence indicting "tar" and nicotine is not based on study of these stubstances but rests on the association betwen "smoking" and disease.

Ample experimental work demonstrates a lack of correlation between amounts of "tar" and nicotine and toxic effects of smoke, as measured by ciliastatic effect, irritation of tissues, and general toxicity, and chemical analysis of smoke shows the presence of many toxic substances besides nicotine. There are known pathogenic mechanisms through which such substances having the described toxic effects can cause emphysema, cardiovascular disease, and cancer.

What then do we propose as minimum standards for nonharmful cigarettes?

Such criteria are chemical and experimental and are categorized as:

1) Standards establishing harmlessness with regard to cancer.
2) Standards establishing harmlessness with regard to emphysema.
3) Standards establishing harmlessness with regard to cardiovascular disease.

From the point of view of cancer, chemistry and experimental procedures must be considered.

Chemistry.—Smoke must be free from any known carcinogens, or any unavoidable traces of carcinogens must be balanced by inhibitors of carcinogenesis.

Experimental.—Fresh smoke condensates ("tars") must cause no skin cancer in mice under the most severe conditions, namely in high doses and in the presence of acetone in lifetime mouse studies that include positive controls of smoke condensates from unmodified cigarettes. Absence of co-carcinogenesis must be shown by negative results of skin painting of "tars" in mice primed with benzpyrene with appropriate positive controls.

From the point of view of *cardiovascular disease*, cigarettes must contain a minimum of nicotine and, in experiments on humans, carefully controlled with "unsafe" cigarettes, they must not produce peripheral vascular reactions. Perhaps, in subacute human experiments, such cigarettes should be shown to cause no change in serum fatty acids.

From the point of view of *emphysema*, much more attention must be paid to gaseous irritants. Those irritants now chemically known must be absent in harmless cigarettes. Exposure of alveolar macrophages must be without effect. Gaseous smoke constituents should have low ciliatoxic effect and the lowest possible acute toxicity. In granuloma pouches and by pellet insertion tests, safe smoke must be nonirritant in doses close to those inhaled by man.

At least two of the groups represented at this meeting have already published evidence that cigarettes far less carcinogenic in animal tests than the conventional product are already on the market. Every type of the experimental tests mentioned reveals a wide variability of toxicity in various brands, some of which had very low values.

If scientists could agree on chemical and experimental standards for a harmless cigarette, quite likely industry could meet them with presently available technology.

F. HOMBURGER

Because the specific tobacco "tar" components that cause cancer in man are not known, and in view of the information presented at this workshop, we recommend that the following steps be taken to help in the establishment of less dangerous cigarettes.

1) Cigarettes should be labeled as hazardous to health, and their "tar" and nicotine content should be listed on the package.

2) Minimum standards of effectivenes for cigarette filters should be set.

3) A maximum permissible "tar" yield of 15 mg per cigarette should be established until the safety of cigarettes with greater "tar" yield can be proved.

4) A minimum butt length (30 mm) should be designed into cigarettes.

5) Minimum quality standards for all components of the cigarette (tobacco, additives, flavorings, etc.) should be established so that the final product is free from contamination by such materials as pesticides (as is the present practice for foodstuffs).

6) Manufacturers should be encouraged to redesign cigarettes so that smokers would be less likely to inhale (*e.g.*, like cigar smoke).

These proposed steps are not the final answer to the problems of smoking and health which face us today. They will have to be modified as our knowledge of cigarette smoke and its relationship to consumer health is increased. But prudence dictates that we take such steps at the present time so that this serious public health problem may be controlled.

GEORGE E. MOORE, M.D., PH.D.
FRED G. BOCK, PH.D.

Having participated in this work group and considering the evidence on the toxicology of cigarette smoke and its constituents, we would like to make the following statement:

Our belief, based upon the scientific knowledge available at present, is that the only way to reduce the harmful effect of cigarette smoke is to decrease the over-all exposure. This can either be done by a reduction of the number of cigarettes smoked or by the use of filter cigarettes, provided that the reduction brought about by the filter will be equal in effect to the reduction in dose obtained if the number of cigarettes is reduced.

We feel that further research to elucidate the relative toxicity of various compounds and combinations thereof in the smoke is a most important and urgent task. The requirements expressed in this group with respect to experimental and epidemiological techniques should be taken into consideration.

Tore Dalhamn, M.D.
Ragnar Rylander, M.D.

As regards the harmful cardiovascular consequences of the cigarette habit, the best available evidence incriminates mainly the nicotine in smoke. The "tars" and other constituents, while of paramount importance in respiratory disease, seem less so in respect to cardiovascular ill effects. It would seem reasonable, therefore, to advocate a denicotinized cigarette. This is clearly within the capability of the cigarette industry today.

As regards the pulmonary as well as the cardiovascular consequences of the cigarette habit, the ideal solution would be a shift to the use of non-inhaled forms of tobacco such as the cigar and pipe. Advertising techniques so successfully employed by the enterprising tobacco industry to promote the use and inhalation of cigarette smoke could be shifted to emphasize the use of noninhaled cigar and pipe tobacco. While some hazard exists in connection with the use of even these forms of tobacco, this is far below that associated with inhaled tobacco.

As regards the cigarette itself, the trend to longer cigarettes is regretable and should be reversed. Larger and more efficient filters, if introduced gradually over a number of years, would likely be accepted by the majority of smokers. The development of such devices on a denicotinized cigarette should be encouraged with some minimum standard imposed.

WILLIAM B. KANNEL, M.D.

SUMMARY OF WORKSHOP

In 1964, the Surgeon General's Committee on Smoking and Health called for remedial measures to reduce the health hazard associated with cigarette smoking. One of these measures is the establishment of a less harmful cigarette.

The proceedings of the workshop dealing with this area indicated significant progress in the identification of factors in cigarette smoke that contribute to the health hazards as well as means of their reduction.

Since a dose-response relation is indicated for the number of cigarettes smoked and the incidence of diseases of the cardiovascular and pulmonary systems, anything that will reduce total smoke exposure is likely to be followed by a reduction in risk. Such a reduction may be expected more rapidly for cardiovascular than for neoplastic disease.

When considering myocardial infarction, the preponderance of evidence suggests that nicotine plays an essential role in its pathogenesis and that its reduction would be associated with a reduction in deaths from this disease. The effect of nicotine on myocardial infarction was attributed to its possible effects on blood coagulation and on mobilization of free fatty acids. The particulate matter in tobacco smoke is clearly carcinogenic to the experimental animal and specific carcinogenic and co-carcinogenic components have been identified. There was a body of opinion that the gaseous phase in cigarette smoke might also affect the pathogenesis of lung cancer and chronic pulmonary disease and that a reduction of all potential toxic substances should be accomplished. There was some disagreement as to the relative importance of various toxic substances in cigarette smoke, particularly as these affect man.

Adequate means for a practical lowering of "tar" and nicotine levels of cigarettes are already available. In fact, there has been a trend toward a quantitative reduction of these smoke constituents in American cigarettes during the past decade. Means are also available to reduce gaseous components.

The tobacco industry needs to be persuaded to manufacture less harmful cigarettes and to increase the acceptability of such cigarettes with that portion of the public that cannot give up smoking. Such measures include:

1. Regulatory standards for a cigarette to be called a "filter" cigarette.
2. Regulatory standards providing that a filter and the nonsmokable overwrap should be not less than 30 mm long.
3. Regulatory standards governing the yield of "tar" and nicotine and, possibly, other smoke components.
4. Regulatory listing on all packages of the "tar" and nicotine content and, perhaps in the future, of other deleterious substances.
5. Encouragement of the design of cigarettes that reduce the practice of inhalation.

It was suggested, based on extensive experimental data, that increased nitrate levels in tobacco would reduce the formation of carcinogenic hydrocarbons.

The workshop members expressed a desire for closer cooperation with each other. It was suggested that research workers interested in the problem of creating a less harmful cigarette form a work group composed of representatives from research groups of universities, industry, private institutions, and the U.S. Government. It is hoped that this group will keep in communication with the Task Forces on Lung Cancer and on Smoking and Health.

Some concern was expressed about claims for new filters or processes to reduce the health risk of cigarette smoking in cases where such claims have not been accompanied by well-documented scientific data. It was suggested that the Public Health Service establish a panel with the necessary scientific background and give it legal authority to protect patent rights in order to evaluate such claims.

Efforts must be continued to develop chemical and biological methodology to establish the relative importance of toxic substances in tobacco smoke and provide guidelines for permissible levels of these substances in cigarette smoke.

The ultimate proof of a less harmful cigarette must be the human experience. It was suggested—and it seems feasible—that a surveillance system be established in several major hospitals in the United States and abroad where the smoking habits of individuals with diseases now known to be associated with cigarette smoking would be recorded. Such records would include the brand of cigarettes smoked by each individual. In this manner the relative health risk associated with a particular type of cigarette could well be established. Members of the workshop agreed to initiate such a system, hopefully with the support of public health agencies.

Having observed man's apparent difficulty in giving up smoking and preventing youth from starting, it is evident that, for practical as well as academic reasons, work on the less harmful smoking products must be continued and extended. It represents one of the logical measures called for by the Surgeon General's Report. Members of the workshop believe that, if properly pursued and supported, and if its suggestions—many of which are practical today—materialize, this remedial measure will make its contribution to our common goal, the reduction, if not elimination, of all diseases linked to cigarette smoking. It is toward this goal that the Workshop, "Toward a Less Harmful Cigarette," hopes to have made a contribution.

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