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Division: Chemical Research
RDM, 1962, No.

Notebook pages: none
Previous Reports:
RDM, 1954, No. 31
RDM, 1955, No. 13
RDR, 1956, No. 10
RDR, 1959, No. 1
RDM, 1962, No. ___

No. of pages: :

THE SMOKING AND HEALTH PROBLEM -- A CRITICAL AND OBJECTIVE APPRAISAL OF

The cigarette smoke-health problem is discussed in detail, and it is related to the potential involvement of the members of the Company's Research Department. Arguments and conclusions by those claiming cigarette smoke as a health hazard, as well as counter-arguments and conclusions by those not in accord with such views are presented. The weight of the arguments and counter-arguments is discussed in some detail. An attempt has been made to present the arguments and conclusions as objectively as possible. Based on these arguments and conclusions, several recommendations are made.

This report is an extension of a companion memorandum (77) which presented my position as briefly and as concisely as possible. The two memoranda have identical schematic organizations. As mentioned before (77), if requested, a thorough, fully documented exposition of the ideas will be prepared.

MEMORANDUM

Although the major part of the sales of this Company consists of cigarettes, what the Company sells is cigarette smoke. To maintain our first-place position against any eventuality, we should be first in acquisition of information concerning the composition and physiologi effects of cigarette smoke.

During the past two decades, cigarette smoke has been the target of a host of studies relating it to ill-health and particularly to lung cancer. The majority of these studies incriminate cigarette smoke from a health viewpoint.

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I. The Evidence - Pro and Con

The cigarette smoke-lung cancer problem has been investigated epidemiologically, pathologically, biologically, and chemically. Each discipline has yielded pertinent information. The epidemiological studies have also suggested a relationship between cigarette smoking and other diseases.

a. Epidemiological Data

It has been shown in thirty retrospective (27*, 38, 104, 118) and in four prospective statistical studies (15, 27*) that the incidence of lung cancer is low in nonsmokers, proportional to cigarette consumption, greater in cigarette smokers than in cigar or in pipe smokers (who show a higher incidence of oral cancer than do cigarette smokers), greater in cigarette smokers who inhale than in those who do not inhale, greater in cigarette smokers continuing the habit than in ex-cigarette smokers, and comparable in male and female cigarette smokers when smoking duration, amount, and tumor type are considered (39, 117). These findings indicate that cigarette smoking increases the risk of developing lung cancer. Many authorities believe the relationship to be one of cause-and-effect.

Contradictory data have been provided by statistical studies which suggest that smoking habits (and possibly lung cancer) are linked to a constitutional factor. The twin studies of Friberg et al., (36), Fisher (34, 35), and Raaschou-Nielsen (65) indicated a greater concordance of smoking habits between identical twins than between fraternal twins. These studies, however, fall in the

*This author reviews 27 different retrospective studies by Breslow, et al., Denoix and Schwartz, Doll and Hill, Haenszel et al., , Koulumies, Levin et al., Lombard et al., McConnell et al., Mills and Porter, Muller, Potter and Tully, Sadowsky et al., Schairer and Schöninger, Schrek et al., Schwartz et al., Stocks, Stocks and Campbell, Wassink, Watson and Conte, Wynder and Cornfield, Wynder and Graham, Wynder and Lemon.

**This author reviews the prospective studies by Doll and Hill, Hammond and Horn, and Dorn.

same category as some retrospective lung cancer-smoking studies, i.e., careful but limited. The Seventh Day Adventist study of Wynder et al. (120) provides serious argument for the constitutional hypothesis. Other contradictory data were provided by the immigration (and also retrospective) studies of Eastcott (31) in New Zealand and Dean (28, 29) in South Africa. These studies compared national averages of cigarette consumption with lung cancer mortality data for immigrants and nonimmigrants. I.e., in the lung cancer victims the actual smoking habits of immigrants to New Zealand and New Zealand-born persons were not known; similarly for the South African study. To validate his findings, Dean (29) obtained smoking data on his sample by questionnaires addressed to the next of kin, a practice decried in several of the retrospective lung cancer-smoking studies. Nevertheless, the results of these studies (28, 29, 31) can account for only a small fraction of the lung cancer incidence observed between smokers and nonsmokers.

The statistical data from the lung cancer-smoking studies are almost universally accepted. The majority of scientists accept these data as indicative of either a high degree of association or a cause-and-effect relationship between lung cancer and smoking. Controversy is provided by Fisher (34, 35), Berkson (14), Little (53A), Greene (37), and others. More will be said about their comments in a subsequent section.

After more than ten years of argument on methodology, sampling bias, retrospective vs. prospective study, inhalation vs. noninhalation, real vs. apparent increase in lung cancer incidence, short butt-length vs. long-butt length, etc., criticism of these studies has been reduced to the dictum A statistical study cannot prove a cause-and-effect realtionship between two factors.

b. Pathological Data

The following observations have been made:

(a) Cigarette smokers' lungs show profound cellular changes (squamous metaplasia, basal-cell hyperplasia, and other atypias) which are proportional to cigarette consumption (4), these changes decrease progressively in the lungs of ex-cigarette smokers in proportion to the time interval

between cessation of smoking and death (5), and similar changes develop in the lungs of mice exposed to cigarette smoke (50-52).

(b) Fluorescent constituents of cigarette smoke are absorbed into respiratory tract cells of man and experimental animals (59, 60). However, fluorescence and carcinogenicity are not synonymous (17). Carcinogenic polycyclic hydrocarbo (benzo[a]pyrene, dibenz[a,h]anthracene) and noncarcinogenic polycyclic hydrocarbons (anthracene, phenanthrene) are highly fluorescent; carcinogens like urethane, p-benzoquinone, and β-naphthylamine exhibit little or no fluorescence.

(c) Whole cigarette smoke (46) and some of its constituents (phenols, fatty acids) (33, 119) cause ciliary paralysis.

(d) Cigarette smoke collects at cilia-free areas and at areas of paralyzed cilia (33, 41).

Contradictory evidence indicates the following:

(a) The above-described cellular changes can be caused by previous respiratory diseases such as influenza (2), pneumonia (107), Asiatic influenza (30), and pulmonary infarcts (6), and by illnesses like uremia (105, 107) and vitamin deficiency.

(c) These changes are observed to a degree in infants (3), in nonsmokers (43), and in residents of areas of extreme air pollution (106, 110).

(b) These changes are observed in the tracheas (windpipes) of smokers, but cancer of the trachea is extremely rare (43-45, 109, 115).

(d) Ciliary paralysis can be caused by air pollutants like industrial gases (25, 112) and automobile exhaust gases (112)

(e) There is no evidence that these changed cells ever become cancerous (40).

These findings may be summarized as follows: Since cellular

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changes in the lung and ciliary paralysis can be caused by factors other than cigarette smoke, since these changes occur in nonsmokers' lungs and in the cancer-free trachea of smokers, and since it is not known whether these changed cells become cancerous, cigarette smoke, therefore, is not he only factor to be blamed in lung cancer causation.

c. Biological Data

Cigarette smoke condensate is carcinogenic to mouse skin (27*). Much is made of the fact that the dosage level used exceeds that of the human exposure. Other investigators like Passey, Orr, Moore and Miller (27**) did not obtain positive results with nominal dosage levels. Some interpret this an indication that cigarette smoke is not carcinogenic. It should be noted, however, that many attempts were made to induce cancer in animals with coal tar prior to the first success with highly unrealistic dosages (121). Kennaway (44) commented on these negative findings as follows:

> "The emphasis laid upon the collected negative results of painting experiments from various laboratories, and the more or less explicit suggestion that these discredit Wynder's results....., suggest that....., where smoking is concerned, the comparison of evidence from man and from animals may not always be conducted with complete impartiality. Positive results, if obtained by legitimate means, must take precedence of negative results."

Cigarette smoke condensate is a powerful promoting (or cocarcinogenic) agent for polycyclic hydrocarbons (102).

Inhalation studies with cigarette smoke have yielded an increased incidence of adenomas in adenoma-susceptible mouse strains (32, 61). No human-type carcinomas have been produced although cellular changes and bronchitic conditions have (50-52).

It is interesting to consider the studies of Campbell (see (108))

*This author reviews the studies by Croninger and Suntzeff, Guerin and Cuzin, Koprowska, Moore and Bock, Orris et al., Sugiura, Wynder et al.

**This author reviews the studies by Passey, Orr, Moore and Miller.

... no one doubts that [chromium compounds] are carcinogenic to the human

who obtained no increased lung tumor incidence in mice inhaling either automobile exhaust gases or cigarette smoke. Subsequent study by others has shown that inhalation of exhaust gases and atmospheric dusts increased the adenoma incidence. Campbell's negative findings with cigarette smoke are often quoted as demonstration of the noncarcinogenicity of cigarette smoke; seldom is his evidence quoted to indicate the noncarcinogenicity of air pollutants!

These negative inhalation results are interpreted by some as an indication that cigarette smoke is not a carcinogen for human lung tissue. Two facts offset such thinking. First, mice are not men, hence carcinomas should not be expected in a host resistant to the induction of carcinoma of the lung, and whose usual lung cancer is the adenoma (108). Also, asbestos and sodium arsenite, recognized industrial carcinogens, have not been shown to be carcinogenic in animals (16). Secondly, the ratio, lung cancer deaths:total cigarette smokers in the United States is approximately 1:1700, hence an inhalation experiment involving mice would require 1700 animals for the production of one carcinoma, assuming that the response of mouse and human lung tissue was the same. No such number has been used in any single experiment. The biological findings are dismissed by some with the statements Mice are not men and Mouse skin is not human lung tissue, statements to which even the proponents of the cigarette smoke-lung cancer proposition agree (116).

d. Chemical Data

Cigarette smoke contains fourteen polycyclic hydrocarbons (27*) and three heterocyclic nitrogen compounds (113) known to be carcinogenic to mouse skin. The hydrocarbons include benz[a]anthracene, benzo[ghi]perylene, benzo[a]pyrene, benzo[e]pyrene, chrysene, dibenz[a,h]anthracene, 1-methylpyrene, cholanthrene (84), dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, dibenzo[a,l]pyrene, 2,3-dihydro-1H-benzo[a]cyclopent[h]anthracene, 10,11-dihydro-

*This author discusses all the polycyclic hydrocarbons except cholanthrene.

9H-benzo[a]cyclopent[i]anthracene, and benz[e]acephenanthrylene. The heterocyclic nitrogen compounds are 7H-dibenzo[c,g]carbazole, dibenz[a,h]acridine, and dibenz[a,j]acridine.

Cigarette smoke also contains various promoting (or cocarcinogenic) agents like the phenols and the fatty acids.

These findings, at first impugned, are now accepted but dismissed as unimportant because none of the compounds has been shown to be carcinogenic or cocarcinogenic to human lung tissue. It is unlikely that such experiments will ever be carried out.

e. The Evidence to Date

Obviously the amount of evidence accumulated to indict cigarette smoke as a health hazard is overwhelming. The evidence challenging such an indictment is scant. However, the evidence from epidemiological, pathological, biological, and chemical studies supporting the proposition that lung cancer is caused by or associated with cigarette smoke is paralleled by similar evidence supporting the proposition that lung cancer is caused by or associated with air pollutants. In some instances, the evidence seems to be stronger in support of cigarette smoke as a causative or associated factor; in other instances, the evidence seems to be stronger in support of air pollutants as a causative or associated factor.

Any criticism levelled at the lung-cancer-cigarette-smoke proposition, e.g., statistical studies cannot prove cause-and-effect relationship between two factors (a criticism of the epidemiology); mice are not men (a criticism of the biological evidence); metaplasia and hyperplasia do not become cancerous (a criticism of the pathological evidence); and no experimental evidence exists to show that any cigarette smoke constituent is carcinogenic to human lung tissue at the level present in cigarette smoke (a criticism of the chemical evidence), is equally applicable to the lung cancer-air pollutant proposition.

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II. Interpretation of the Evidence

After reviewing this evidence, many governmental health agencies and medical societies throughout the world have concluded that it was sufficient to establish a cause-and-effect relationship between cigarette smoking and cancer of the lung. None stated that cigarette smoke was the cause, the only cause, etc., and many acknowledged the role of air pollutants in the increased incidence of lung cancer. None suggested that research on all other factors be dropped in favor of a concerted study of cigarette smoke. These agencies included the American College of Chest Physicians (1), the British Ministry of Health (27*), the British Medical Research Council (27*), the Danish Joint Committee of the Danish National Health Service, Danish Cancer Society, and the Danish Medical Association (26), the National Cancer Institute of Canada(27*), the Netherlands Ministry of Social Affairs and Public Health (27*), the Royal College of Physicians (Gt. Britain) (103), the United States Study Group on Smoking and Health 1957 (27*), the United States Public Health Service (27*), the World Health Organization (27*), etc.

Commenting on such pronouncements, Little (56), Scientific Director, TIRC, said

> "We will not find out from over-simplified and perhaps superficial conclusions as to causation. Such an attitude would only stifle or delay needed research to find the basic origins of lung cancer and cardiovascular diseases, which are most powerful, diversified and deadly enemies to our well-being. Nor will they be solved by resolutions or by review committees that concern themselves solely with suggestive or incomplete data."

At present in the United States, this evidence is under review by two groups, the Surgeon General's Advisory Committee on

* This author summarizes these opinions.

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Smoking and Health and by a special committee of the American Medical Association. It will be very surprising if their conclusions differ substantially from those of other groups cited.

It has been repeatedly stated that some scientists discount the cigarette smoke-lung cancer theory. This is true. But it should be noted that many of those quoted in this regard are on record with contrasting views. Scientists in this category include, among others, Arkin, Berkson, Dean, Eastcott, Fisher, Hueper, Little, Macdonald, Passey, Rigdon, and Rosenblatt.

Berkson is repeatedly quoted as one of the statisticians disagreeing with the cigarette smoke-lung cancer data. However Berkson's considered opinion is illustrated by his statement (13):

> ".....the definitive important finding of these prospective statistical studies is not that there is an association between smoking and lung cancer, but that there is an association between smoking and deaths from all causes generally....."

The thesis that cigarette smoking was statistically associated with a shortened life span was advanced almost a quarter of a century ago (64).

The statistical studies by Dean (28, 29) in South Africa and Eastcott (31) in New Zealand cannot carry the weight ascribed to them. Eastcott's study (31) did not compare immigrant and nonimmigrant lung cancer victims with respect to their individual smoking habits but with the yearly per capita consumption in New Zealand and the United Kingdom. Since the per capita tobacco consumption was greater in New Zealand than in the United Kingdom and since the number of immigrant lung cancer victims was greater than the number of nonimmigrant lung cancer victims in New Zealand, Eastcott concluded that smoking did not contribute to his findings. Similarly Dean (28) did not compare individual smoking habits. Later, he (29) ascertained the smoking habits of the lung cancer victims by questionnaires addressed to the victims' next of kin, a procedure criticized previously by reviewers of the retrospective lung cancer-smoking studies.

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Kotin, member of the Scientific Advisory Committee, TIRC, recently commented (46) on the conclusions of the 1957 U. S. Study Group on Smoking and Health:

> "The statement.....to the effect that 'The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoke is a causal factor in the rapidly increasing incidence of human epidermoid cancer of the lung' represents a view with which we concur."

Little, Scientific Director, TIRC, stated in 1947 (53, cf. 55):

> "Although no definitive evidence exists concerning the relation between the use of tobacco in the instance of lung cancer, it would seem unwise to fill the lungs repeatedly with the suspension of fine particles of tobacco products of which smoke consists. It is difficult to see how such particles can be prevented from becoming lodged in the walls of the lungs, and when so located, how they can avoid producing a certain amount of irritation. One might also question the ultimate results of continued inhalation of the type of atmosphere which characterizes the lower levels of city streets. Experimental work with animals involving these matters is still inconclusive, but it seems probable that the lung as an organ is not immune to the effect of chronic irritation and that it will in this respect resemble the other organs of the body. Such being the case, wisdom in avoiding unnecessary lung irritation seems to be established."

and more recently (58):

> ".....in the first place we don't criticize the statistical findings. We believe that they were honestly obtained and that they show, under the conditions that they were collected, a strong correlation which is suspicious enough to make it imperative that further research be carried on....."

Hueper, long a proponent of the lung cancer-air pollutant proposition, noted (42):

> "A definite amount of reservation is indicated in accepting the claims advanced by some parties concerning the role of cigarette smoking as a direct or indirect factor in the causation of lung cancer. Nevertheless the type and amount of evidence on this matter on hand justifies the conclusion that cigarette smoking has contributed to or aggravated the action of other carcinogenic respiratory pollutants by producing especially functional disturbances in the bronchial mucosa.....It would be most unwise, on the other hand, if, through an exaggerated emphasis placed on the significance

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> of cigarette smoking, the study....of air pollutants would be impaired and neglected. The available evidence rather definitely assigns to these factors an important role as human respiratory carcinogens."

And Passey (63), who does not believe that lung cancer results from the action of carcinogens, says:

> "I do not belittle the important part which smoking plays [in lung cancer causation] . My aim is to suggest its mode of action. In fact, I would say that it is dangerous to smoke."

Additional citations could be given but these few suffice for now.

III. The Tobacco Industry's Contribution

To investigate the cigarette smoke-health situation The Tobacco Industry (except for Liggett and Myers Tobacco Company) has given about five million dollars to TIRC since 1954 for research. According to Little,(54), its Scientific Director, the purpose of TIRC is

> "....to encourage and support qualified research scientists in their efforts to learn more about these complex problems [cancer and heart disease] ."

Through December 1961, TIRC grantees published 197 papers (56, 57). Of these, 36 were concerned with the chemistry of tobacco and its smoke; 47 with cancer research; 13 with human lung studies; 78 with heart and circulation studies; 4 with gastrointestinal tract studies; 5 with psycho-physiological studies; and 14 miscellaneous studies (lung cancer reviews, tobacco-health textbook).

I believe that much of this research, particularly that on the chemical, biochemical, and biological study of tobacco and its smoke, could have and should have been carried out in the research departments of the tobacco companies*.

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* One TIRC grantee isolated and characterized 6-hydroxynicotine and subsequently published his findings. A similar study was carried out in this Company's Research Department. Other grantees have investigated insecticide residues on tobacco, substitued coumarins (esculetin, scopletin) in tobacco and smoke, etc.

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The members of this Company's Research Department are as qualified, as objective, and as interested in learning "....more about these complex problems..." (to quote Little (54)) as scientists not employed by a tobacco manufacturer.

Concerning qualification of research persons, it is interesting to note the criticism of cigarette smoke inhalation studies (presumably those of Essenberg) by Little in 1957 (55):

> "These poor beasts are usually put in practically an air tight container, and smoke is pumped in and pumped in in such quantities that the white rats become yellow ....or yellowish brown...."

and to relate this criticism to observations made (51) in similar cigarette smoke inhalation studies (50-52) conducted by a TIRC grantee:

> "Depending on the time of exposure, the fur of the exposed mice gradually changed from white to yellow to darkish brown...."

This smoke inhalation project was activated on September 1, 1957, over a month after Little's criticism of such techniques.

If a coordinated chemical, biochemical, and biological research program on the tobacco-health problem were undertaken by the members of this Company's Research Department, the findings made could not have any more adverse effect on the Tobacco Industry in general or on this Company in particular than those reported (56,57) by TIRC grantees or associates, Kotin and Falk (paralysis of cilia with cigarette smoke and ~~cigarette smoke~~ components), Leuchtenberger (cellular changes produced in the lungs of mice exposed to cigarette smoke), Bock, Moore, and Homburger (tumor production with cigarette smoke), Kosak (isolation of carcinogenic

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compounds from cigarette smoke), etc. It may be advantageous in the future for our Research Department personnel to have experience in studies involving test mammals, particularly if governmental restrictions are imposed because of conclusions reached by the recently appointed Surgeon General's Advisory Committee on Smoking and Health. One of the five observers at the first meeting of this Committee was a Division Director of the Food and Drug Administration. Members of this Research Department have studied in detail cigarette smoke composition (8, 9, 18-24, 47-49, 68-77, 79-101, 114). Some of the findings have been published (19, 22, 24, 74, 80, 82, 89A, 91, 94, 96, 98, 100). However, much data remain unpublished because they are concerned with carcinogenic or cocarcinogenic compounds (23, 47, 48A, 68-72, 75, 76, 78, 84-86, 88, 92, 101, 114) or with patentable material (83, 89). This raises an interesting question about the former compounds. If a tobacco company plead "Not guilty" or "Not proven"* to the charge that cigarette smoke (or one of its constituents) is an etiological factor in the causation of lung cancer or some other disease, can the company justifiably assume the position that publication of data pertaining to cigarette smoke composition or physiological properties should be withheld because such data might affect adversely the company's economic status when the company has already implied in its plea that no such etiologic effect exists?

It is not my intent to suggest that this Company accept the

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* E.g., Lartigue vs. Reynolds Tobacco Co. and Liggett and Myers Tobacco Co., Greene vs. American Tobacco Co., and Pritchard vs. Liggett and Myers Tobacco Co.

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cigarette smoke-health data at face value, but I do suggest that this Company, through its Research Department, actively participate in cigarette smoke-health studies. Other Companies (General Motors Corporation (7), Imperial Tobacco Company (Great Britain) (10-12)) have reported their findings on the air pollution-health problem and cigarette smoke-health problem, respectively, without apparent loss of prestige (or income).

IV. Recommendations

After consideration of the evidence available on the cigarette smoke-health problem and the Company's obligation* to its customers, stockholders, and employees, it is recommended that facilities, animals, and personnel (where necessary) be acquired to study biologically cigarette smoke, tobacco, tobacco and additives.

This recommendation has been made previously by Teague (111) in 1953, by Rodgman in 1954 (66), in 1955 (67), in 1956 (68A), in 1959 (72), and in 1962 by Nielson (62) and Rodgman (77). Data from such studies may be invaluable if governmental restrictions are imposed as a result of the conclusions of the Surgeon General's Committee on Smoking and Health. It is, I believe, more urgent than ever that we acquire dexterity in biological techniques.

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* It is interesting to note remarks like "Why don't 'they' do something about the liquor industry? After all, there are an estimated four million [illegible] classified as alcoholics. Alcoholism is not only is a health hazard to the drinker but also causes untold anguish to his family." or "What about the meat-packing industry and the supposed relationship of saturated animal fat to cholesterol-caused circulatory disorders and heart disease? After all, many more persons die of heart disease than lung cancer." These remarks may have some justification, but attempts to minimize our obligations by pointing an accusing finger at others is no solution to the cigarette smoke-health problem!

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It is recommended that data already available on physiologically active cigarette smoke components, e.g., polycyclic hydrocarbons, phenols, be published. It is also recommended that analytical procedures concerning such components be published.

These recommendations are made because I believe they represent the best answer to the questions: What effect would immediate publication of these data have on this Company's economic status? What would be the effect on this Company of not publishing these data now, but being required at some future date to disclose such data, possibly in the unfavorable atmosphere of a lawsuit?

It is recommended that the Company's supervisory personnel be provided with reports like the Royal College of Physicians' report Smoking and Health, the Annual Report of the Scientific Director (TIRC), and other pertinent review articles just as they were provided with Northrup's book Science Looks at Smoking, the pamplets Tobacco and Health, and "favorable" articles such as the one from Life entitled New Evidence That Cancer May Be Infectious. In this way, the Company's supervisory personnel will be better informed about the cigarette smoke-health problem than they would be if their main information sources were the daily newspaper, Reader's Digest, etc.

And finally, it is recommended that the Company's management recognize that many members of its Research Department are intensely concerned about the cigarette smoke-health problems and related eager to participate in their study and solution.

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