A Critical Reassessment of the Evidence Bearing on Smoking as the Cause of Lung Cancer

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The controversial claim that cigarette smoking is a significant cause of lung cancer is challenged in this critical reappraisal of some important population studies.

Introduction

Many substances existing in significant quantities in the industrial and community environment possess considerable carcinogenic potential. For example, recent National Cancer Institute-sponsored experiments with 120 commonly used chemicals found that 11 induced a significantly elevated incidence of tumors and 20 gave results that called for further evaluation.[1] Another recent survey found that "We can now reproduce essentially a wide spectrum of tumor responses in the different segments of the respiratory tract, from the nasal cavity down to the alveoli, and correlate them with chemical activity of different carcinogens" (p. 325 in Reference 2). A number of experimental results on the oncogenic role of organic compounds that were puzzling for some time are better understood now. For instance, only relatively recently has it become clear that the carcinogenic properties of soot samples depend on the extent to which they carry benz[*a*]pyrene and other aromatic hydrocarbons.[3] Also, it appears to be necessary for carcinogens to be brought into prolonged contact with lung tissues through particles of the right size, as those resulting from the incomplete combustion of organic fuels,[4,5] or to injure the epithelium through use of toxic vapors simultaneously with the introduction of carcinogens (as high concentrations of SO_2 or by the use of some halogenated ethers).[6]

On the other hand, the belief that smoking is a major cause of lung cancer still lacks definitive experimental demonstration but depends almost exclusively on the result of statistical surveys. The designs and execution of these surveys have been severely criticized (as well as hotly defended) in the past, and the discovery that the antecedents of lung cancer are found in many alternative and interactive causes may again create the need to reevaluate the results of these epidemiological studies.*

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* In part, a number of instances of reevaluation are on record already. The recent report by the Committee on Biological Effects of Atmospheric Pollutants has concluded that, after all, particular polycyclic pollutants may play a major role in the etiology of many cancers including lung cancer, although the primary burden still is placed on cigarettes.[7] Unfortunately, the National Academy of Sciences report falls far short of a critical evaluation of lung cancer studies.[8]

These needs are further strengthened by data released after the report of the Surgeon General's committee, *Smoking and Health.*[9] These data suggest that there is a serious possibility that the apparent association between smoking and lung cancer observed in population studies, particularly that found in the two crucial studies conducted by the American Cancer Society (ACS), is possibly a spurious result of the selection procedure by which the study populations were assembled. This conclusion is further strengthened by the results of a prospective study started in 1965 comparing over a quarter million Japanese smokers and nonsmokers. This Japanese study avoided some of the "volunteering" aspects in the selection of subjects (and, with it, a major source of bias). One even more significant observation is that the lung cancer incidence in England and Wales, in Scotland, and in the United States appears to have leveled off and begun to decline for all but the older populations. For British males this decline appears to have started prior to 1955 for the age groups up to 44, prior to 1957 for the age groups 45 to 54, and prior to 1964 for the age groups 55 to 64 years of age. In the U.S. the same decline, somewhat less pronounced, also started approximately in 1955 but was restricted more to younger age groups. It is unlikely that this decrease can be related to a decline in smoking dating to 1965, especially if the latent period for tumorigenesis is 15 to 30 years (a reasonable estimate based on tumorigenic responses of man to known carcinogens). Neither can it be attributed to any decrease in cigarette tar and nicotine levels since it is reported that the reduction of tar and nicotine levels began in the 1950s[10] and the popular use of the filters postdated 1955.

The ACS Study Population Appears to Have Been "Selectively" Assembled

Conclusions concerning the hazards of cigarette smoking were primarily based on seven prospective surveys (p. 81 in Reference 9). They all share the common characteristic that their study populations were assembled through successions of "selection factors" which depended heavily upon the cooperation of, availability of, and ease of access to potential study subjects who also differed in crucial characteristics such as smoking habits, disease, occupational exposure to chemical carcinogens, and so on. The most important of these studies were those conducted by the volunteers of the American Cancer Society. While Dr. Hammond has not permitted public review of the ACS data, and despite the limitations imposed by the scant amount of data published about the actual characteristics of the population, a number of important and extremely remarkable conclusions can be drawn from his publications.*

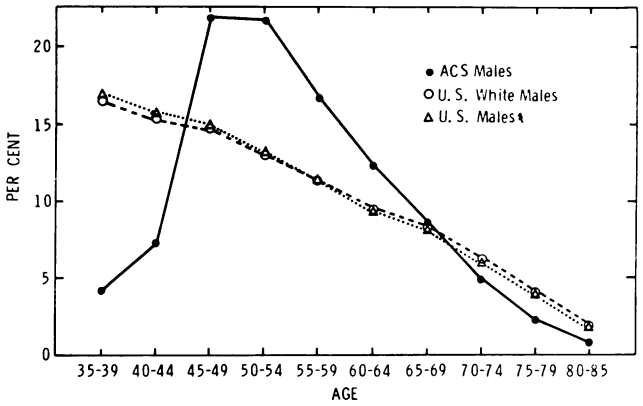

FIGURE 1 Comparison of ACS and U.S. populations: percentage distribution by age. The age distribution of ACS males in 1960 comes from Hammond.[12] Comparable figures for a population of U.S. males between the ages of 35 and 85 were computed from tables given in the 1960 U.S. census report.[13]

Because the ACS population was restricted to households containing at least one adult 45 years of age or older, certain characteristics had to be expected that are peculiar to the population residing in such households. These characteristics are present, but so are other features that betray that the ACS recruitment procedure was strongly influenced by factors associated with the composition of the ACS volunteer group and with their likely attitudes toward smoking and disease. The workings of these special selection processes can be seen by comparing the ACS group to the U.S. population of the 1960 census (the year the study population was selected).

For instance, the ACS population contains approximately 10 per cent fewer males and 10 per cent more females than did the U.S. The age distribution of the ACS population does not have the pyramidal shape one would expect for any cross-cut of a normally aging group (Figures 1 and 2). Other comparisons show that the ACS population is much better educated (Table 1), is much taller (Table 2), contains one-tenth the number of blacks found in the U.S. population, and has a predominance of Protestants and native Americans (Tables 3 and 4). In addition, the rural population is underrepresented, by far, as are various nonindustrial regions of the country (Table 5).

A certain amount of confusion has been created by Dr. Hammond in describing his sampling procedures. His original description of sampling procedures gives the impression that care was taken to obtain a representative sample. "The volunteer workers were so selected as to

* Relevant information is scattered throughout Dr. Hammond's publications and often is given in terms of mortality ratios and rates per 100,000 population, which give little information about how population characteristics are actually distributed. There are also many ambiguities in the published data for which answers are not easy to obtain. An invitation was extended to Dr. Hammond to meet with the advisory panel of our study to discuss ways and means by which the ACS data could be made available for review and, at the same time, how his and ACS's interests and commitments could be safeguarded. This advisory panel was made up of 10 leading scientists and statisticians from as many universities and laboratories. Dr. Hammond declined to participate in this review or to make his data available.[11]

include all segments of the population except illiterate and migrant workers" (p. 4 in Reference 14). But years later the claim is made that "The study population was not intended to be a probability sample of the total population of the United States. Instead, we attempted to enroll a disproportionate number of people from certain selected groups so as

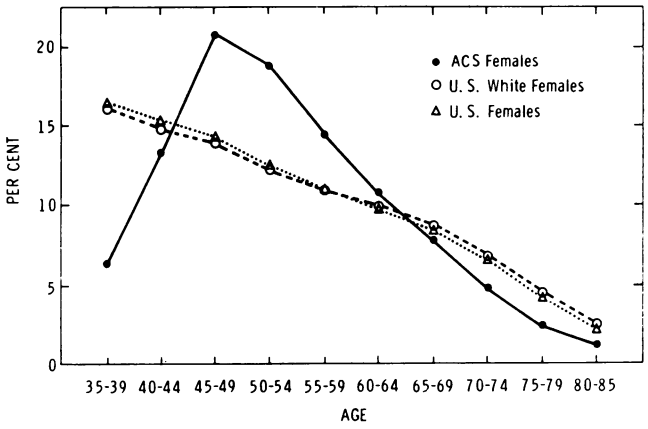

FIGURE 2 Comparison of the ACS and U.S. populations: percentage distribution by age. The age distribution of ACS females in 1960 comes from Hammond.[12] Comparable figures for a population of U.S. females between the ages of 35 and 85 were computed from tables given in the 1960 U.S. census report.[13]

TABLE 1—Comparison of the ACS and U.S. Populations: Percentage Distribution by Educational Attainment

Population	No High School	Some High School	High School Graduate	Some College	College Graduate
ACS* males, ages 45–79	24.30	20.97	17.85	18.10	18.78
U.S.† white males, ages 45–79	54.67	16.78	14.43	7.07	7.05

* Figures for the ACS population were derived from Hammond,[14] Table 2.

† Figures for the U.S. population were derived from U.S. Bureau of the Census,[15] p. 406.

TABLE 2—Comparison of the ACS and U.S. Populations: Percentage Distribution by Height

	Inches				
Population	Under 66	66–67	68–69	70–71	Over 72
ACS* males, ages 45–79	8.57	18.89	26.37	29.30	16.87
U.S.† males, ages 45–79	27.57	26.67	26.29	13.74	5.75

* Figures for the ACS population were derived from Hammond.[16]

† Figures for the U.S. population were derived from National Center for Health Statistics,[17] p. 14.

TABLE 3—Comparison of ACS Male Smokers and the U.S. Male Population (1960) by Race and Place of Birth

Race and Country of Birth	% of ACS Smokers* (Male)	% of U.S. Population† (Male)
Native-born white	94.89	78.80
Foreign-born white	4.20	12.87
Black	0.91	8.33

* Source: Hammond.[16]

† Source: U.S. Bureau of the Census,[15] p. 359.

TABLE 4—Comparison of ACS Male Smokers to the U.S. Male (All Races) Population of 1957 by Religion for Ages 45–79

Population	Protestant	Catholic	Jewish	Total
ACS* smokers, ages 45–79	79.55	17.33	3.12	100.00
U.S.† men, all races, ages 45–79	70.80	24.95	4.25	100.00

* Source: Hammond.[16]

† Source: U.S. Bureau of the Census,[18] p. 8. U.S. data for 1957 were compiled from age groupings 45–64 and 65 years and over.

TABLE 5—Comparison of the ACS and U.S. Populations (1960) of Comparable Ages, by Sex and Place of Residence

Type of Area	% of ACS Men*	% of U.S. White Men†	% of All U.S. Men†
Metropolitan (more than 50,000 population)	61.64	53.22	53.93
Nonmetropolitan (2,500–50,000 population)	17.79	16.12	15.84
Rural	20.57	30.66	30.23
Total	100.00	100.00	100.00

* Source: Hammond.[14] (The 2,093 men reported as "Not Classified" are not used here to compute percentages.)

† Source: U.S. Bureau of the Census,[13] pp. 148–151.

to have sufficient numbers for analysis of death rates within each such group" (p. 2 in Reference 19). But, whatever the reasons, to a statistician, such differences between the U.S. and the largely self-selected population are alarming. The objection is not that the study population was not drawn at random but that self-selection processes may have spuriously created (or at least substantially contributed to) differences between categories of the study population that are not present in the population at large or, vice versa, may hide true differences. After all, the factors determining whether a subject was followed included:

- The zeal of the chapters and of the volunteers to

organize the extensive effort needed to collect the subjects and follow them through time;

- The access volunteers had to friends and others for recruits (many of the ACS volunteer researchers reputedly were doctors' wives with a possible access to patients);
- The feelings, opinions, and motives of the individual volunteer in selecting her subjects;
- The agreement of smokers and nonsmokers, or sick and healthy individuals, to cooperate with the study;
- The ability of the volunteer or the staff member to locate healthy individuals with the same facility as he or she could locate sick persons; and
- The constant publicity concerning cigarette smoking that may have had any number of subtle psychological and sociological effects on selecting out the final group of subjects (or, for that matter, affecting interpretation of the data obtained).

Just how did these selection processes operate with respect to disease and smoking? For instance, did some volunteers of the American Cancer Society, in their zeal and perhaps without being aware of doing so, favor among potential recruits those who smoked and were ill (perhaps even from cancer) and those who did not smoke and were free of disease? Dr. Hammond himself reports that the number of questionnaires in the first prospective study (1952) had to be eliminated because volunteers had noted on the margin that the man selected for study had been already diagnosed with lung (or some other) cancer, despite instructions that such subjects were not to be recruited.[20]

TABLE 6—Percentage of Deaths for Most of Causes for the ACS Female Population and U.S. White, Female Population (1960) by Race and Sex, for Ages 35–84*

Underlying Cause of Death	International List Nos.	ACS Population Females	Comparable U.S. White Females	Comparable U.S. All Females
Lung (excl. trachea, pleura)	162	1.47	0.47	0.45
Buccal cavity, pharynx	140–148	0.30	0.30	0.30
Larynx	161	0.01	0.04	0.04
Esophagus	150	0.12	0.20	0.21
Bladder and other urinary	181	0.47	0.45	0.45
Kidney	180	0.48	0.36	0.33
Prostate	177	—	—	—
Pancreas	157	1.63	1.17	1.13
Liver, biliary passages	155	1.06	0.76	0.70
Stomach	151	1.53	1.52	1.51
Colon, rectum	153, 154	5.23	4.15	3.94
Leukemia	204	1.32	0.88	0.83
Lymphoma, Hodgkin's disease	200–203, 205	1.85	1.07	1.01
Breast	170	9.20	4.98	4.77
Uterus	171–174	2.80	2.70	2.87
Ovary, Fallopian tubes	175	2.76	1.75	1.65
Coronary heart disease	420	32.48	34.13	32.74
Rheumatic heart disease	400–402, 410–416	2.17	1.91	1.80
Hypertensive heart disease	440–443	4.31	5.90	6.71
Other heart disease	421, 422, 430–434	4.21	5.92	6.05
Aortic aneurysm (nonsyphilitic)	451	0.60	0.42	0.41
Cerebral vascular lesions	330–334	14.03	16.56	16.90
Other circulatory diseases	444–447, 450, 452–468	3.11	4.31	4.80
Emphysema	527.1	0.34	0.23	0.21
Gastric ulcer	541	0.25	0.23	0.22
Cirrhosis of liver	581	0.96	1.37	1.35
Diabetes	260	2.51	3.16	3.28
Ill defined diseases	780–795	0.38	0.65	0.97
Violence, accidents, suicide	E800–E965, E970–E999	4.42	4.41	4.37
Total		100.00	100.00	100.00

* In order to construct this table, only those causes of death were used for which deaths in the U.S. population were available for comparable ages. The Hammond data came from Appendix, Table 13 of Reference 12, and the U.S. data from pp. 48–97 in Reference 21. Comparisons were not possible for the following causes of death from Hammond's table: other specified sites, cancer–site not specified, pneumonia, influenza, other pulmonary diseases, duodenal ulcers, nephritis and other kidney diseases, and other specified diseases, involving a total of 2,005 or 12.0% of all deaths reported by Hammond. Hammond's figures for lung cancer exclude involvement of trachea or pleura. However, the figures for the U.S. include it. For 1960 there were only 29 lung cancer deaths with involvement of trachea and pleura for ages 35–84.

TABLE 7—Percentage of Deaths for Most of Causes for the ACS Male Population and U.S. White, Male Population (1960) by Race and Sex, for Ages 35–84*

Underlying Cause of Death	International List Nos.	ACS Population Males	Comparable U.S. White Males	Comparable U.S. All Males
Lung (excl. trachea, pleura)	162	5.01	2.49	2.44
Buccal cavity, pharynx	140–148	0.51	0.69	0.67
Larynx	161	0.25	0.33	0.33
Esophagus	150	0.26	0.52	0.57
Bladder and other urinary	181	0.73	0.81	0.78
Kidney	180	0.54	0.47	0.45
Prostate	177	1.94	1.91	1.97
Pancreas	157	1.45	1.18	1.17
Liver, biliary passages	155	0.54	0.39	0.39
Stomach	151	1.50	1.83	1.88
Colon, rectum	153, 154	3.22	2.84	2.74
Leukemia	204	1.15	0.86	0.81
Lymphoma, Hodgkin's disease	200–203, 205	1.27	1.02	0.99
Breast	170	0.03	0.03	0.03
Uterus	171–174	–	–	–
Ovary, Fallopian tubes	175	–	–	–
Coronary heart disease	420	49.94	45.21	43.20
Rheumatic heart disease	400–402, 410–416	1.33	1.24	1.19
Hypertensive heart disease	440–443	2.50	3.32	3.93
Other heart disease	421, 422, 430–434	3.63	5.22	5.42
Aortic aneurysm (nonsyphilitic)	451	1.53	0.93	0.89
Cerebral vascular lesions	330–334	9.62	11.57	12.00
Other circulatory diseases	444–447, 450, 452–468	2.46	3.35	3.93
Emphysema	527.1	1.84	1.27	1.20
Gastric ulcer	541	0.50	0.67	0.64
Cirrhosis of liver	581	1.20	2.03	1.99
Diabetes	260	1.22	1.68	1.70
Ill defined diseases	780–795	0.47	1.02	1.30
Violence, accidents, suicide	E800–E965, E970–E999	5.36	7.12	7.39
Total		100.00	100.00	100.00

* In order to construct this table, only those causes of death were used for which deaths in the U.S. population were available for comparable ages. The Hammond data came from Appendix, Table 13 of Reference 12, and the U.S. data from pp. 48–97 in Reference 21. Comparisons were not possible for the following causes of death from Hammond's table: other specified sites, cancer—site not specified, pneumonia, influenza, other pulmonary diseases, duodenal ulcers, nephritis and other kidney diseases, and other specified diseases, involving a total of 2,754 or 10.4% of all deaths reported by Hammond. Hammond's figures for lung cancer exclude involvement of trachea or pleura. However, the figures for the U.S. include it. For 1960 there were only 93 lung cancer deaths with involvement of trachea and pleura for ages 35–84.

This not only leaves open the question of just how many such cases were not eliminated in the first study because no notes were made on the margin of the questionnaire but also how many cases of lung cancer were included by volunteers in the second and crucial study of over a million men and women to "vote," so to speak, their confidence that smoking caused lung cancer. (The same may be true for heart disease and emphysema.) Data released by Dr. Hammond in 1966[12] is of utmost significance since it offers considerable support for this possibility. In Tables 6 and 7 we compare the distribution of causes of death for most deaths in the ACS population with the distribution of deaths for the same causes that would be expected from a segment of the U.S. population that was constituted similarly, by age, sex, and race, to the ACS population. We find that the ACS males die from lung cancer proportionately twice as frequently as do U.S. males, and the ACS females die proportionately 3 times as frequently from this disease as do U.S. females. Twice as many females also die from breast cancer, and for males approximately 10 per cent more deaths for coronary heart disease are reported in the ACS than in the U.S. population. Also, ACS males and females die at an increasing rate from emphysema (50 and 40 per cent more, respectively). Note that (with the exception of breast cancer) these are all diseases popularly associated with smoking. (Yet, it is not true that the ACS population died at an overall faster rate than did the U.S. population. The overall mortality in these populations is the same for men and somewhat less for ACS women.)

It is difficult to explain such startlingly peculiar results.

How could one *intentionally* design a selection procedure that would ensure that individuals prone to eventially die from lung cancer somehow are included at twice or 3 times the rate typical for the U.S. population, or which would include 10 per cent more heart disease, or twice as many breast cancer, or 40 or 50 per cent more future emphysema cases? Smoking is ruled out immediately as a possible condition here. The number of smokers in the ACS population is probably smaller than would be true for a representative sample of the U.S. population.*

One reasonable explanation for this peculiar finding is that some of the volunteers selected households with sick individuals, especially those suffering from cancer, heart disease, and emphysema. Such an argument gains special weight if we consider the doubled prevalence of breast cancers among the ACS women. If the volunteers selected women smokers who were already suffering from cancer, such a result as we observe may have easily come about since the number of lung cancers among ACS women is extremely small and that of breast cancers quite large.

It is also possible that the ASC population was assembled by a selection process that may have preferred persons who were in a high respiratory disease or cancer risk group. There are such groups among some occupations, and it is not impossible that selection could have operated in that direction. There is yet one other explanation, at least for the lung cancer deaths, namely, that more than half of the primary lung cancers really were secondary metastases. But this explanation has been ruled out by Dr. Hammond, who is quite specific in reporting his lung cancers as primary and insists that most of the 1,159 male deaths in the second study had specific reports from physicians and that while "it may be that a few of the 1,159 deaths attributed to lung cancer were due to cancer of some other primary site . . . Even so, the evidence would indicate that most of these men (probably nearly all) actually died of cancer originating in the lungs" (p. 150 of Reference 12).†

Were Similar Elements of Bias Present in Other Prospective Studies?

In many ways, the other studies suffered from many of the same multiple selection factors of the ACS study because information about a subject depended primarily upon his willingness to participate in the study or on the investigator's ability to locate individuals who were ill with the same facility as individuals who were not, and so on. It is true that the results of all of these studies are uniformly alike and that is impressive. Whenever smokers and nonsmokers are compared, smokers die with increased incidence from most diseases but especially from lung cancer. But to what extent are these similar results due to similar selection biases? It is difficult to get answers to this question without making the same detailed comparisons to reference populations as we have done with the ACS study and which the authors of other prospective studies have neglected. It would be valuable to know to what extent the veterans in Dorn's[23] or Best's[24] studies are different from the veterans in the U.S. or Canada or to what extent the various workers in the California study[25,26] are different from all workers in the same profession. Additional evidence that study populations are highly selected comes from Doll and Hill,[27] who indicate that physicians in the United Kingdom who volunteered to become part of their study differ from the population of British physicians. The very fact that 30 per cent of the British physicians did not respond to the questionnaire ought to have raised serious concern about the results of Doll and Hill's study. Studies based on the follow-up of individuals who respond to solicitation via questionnaires are very sensitive to biases and for that reason every effort ought to be made in such investigations to intensively study a subsample of the nonresponding population.[28] Doll and Hill never reported the results of such a follow-up attempt nor any other information that would justify the conclusion that the 70 per cent of physicians who responded to their original inquiry do not constitute a highly selected study population.

Because of these shortcomings common to all American, British, and Canadian prospective studies, one new investigation looms with special importance. This Japanese study avoided the dangers of self-selection bias by attempting to obtain information on all individuals over 40 years of age living in particular districts.[29] All adults over the age of 40 in a number of districts were interviewed by trained public health nurses at the time that the National Census took place. The actual number interviewed was very large, 265,118, and is reported to range from 91 to 99 per cent of the reference population in different districts.

While caution needs to be exercised in accepting findings in a population so different in race and culture from the white, Western, European citizens of the other studies, the results reported by Hirayama form an interesting contrast. Table 8 shows that the mortality among Japanese smokers and nonsmokers was largely the same. In fact, during part of the study, smokers died at a lesser rate than did nonsmokers. If we inspect the Japanese data for all diseases in Table 8, the difference in overall mortality between smokers and nonsmokers is far from impressive. The Japanese study offers substantial support for the suspicion that selection bias affected the seven retrospective studies on which *Smoking and Health* bases its major conclusions. It has been pointed out by Berkson[30,31] and also by many other leading statisticians that one indication of biased population selection would be an all-pervasive increased prevalence of smokers' mortality for all disease categories.

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* Comparison groups are not easy to find because of the unusual distribution of the ACS population. The ACS population is nearest in composition to that of employed adults. For a group of employed adults, Dunn found that the percentage of nonsmokers among men in 10 occupations varied from 17 to 28 percent.[22] On the other hand, approximately 33 percent of the ACS males were nonsmokers.

† Nevertheless, it would be interesting to see how subjects classified originally as not specified were apportioned among smokers and nonsmokers.

TABLE 8—Smoking and Total Deaths, 15 Month's Follow-up Result of Prospective Study for 265,118 Adults Age over 40 in 29 Health Center Districts in Japan (January, 1966–March, 1967)*

	Jan.–June, 1966 (First 6 Months)			July, 1966–March, 1967 (Next 9 months)			Jan., 1966–March, 1967 (Total of 15 Months)		
	M	F	Total	M	F	Total	M	F	Total
Actual deaths among smokers	426	60	486	792	104	896	1,218	164	1,382
Expected deaths†	444	52	496	704	88	792	1,148	140	1,288
Ratio actual/Expected	0.96	1.15	0.98	1.12	1.18	1.13	1.06	1.17	1.07

* Source: Hirayama,[29] Table 4.

† Obtained by applying age-specific death rate for nonsmokers to smokers' population by age groups.

And, indeed, this is exactly what was found. *Smoking and Health* reports that of 26 diseases, 25 had mortality ratios of 1 or larger and only one had a mortality ratio of smaller than 1 (p. 102 in Reference 9). However, proponents of smoking/disease links have refused to accept Berkson's arguments. Instead, they have claimed either that specificity does exist, nevertheless, by pointing to the very large mortality ratio for lung cancer[9] and to the fact that a very small number of diseases did not show a higher incidence of mortality for smokers than for nonsmokers,[32] or they have tended to claim that the overall increase in mortality of smokers is due to the ubiquitous effect of smoking.[33] But the Japanese data, which appear to be free from at least one major source of selection bias, fail to find an overall difference in mortality between smokers and nonsmokers (Table 9). Of 37 diseases analyzed, smokers have a higher mortality ratio for 21 and a lower mortality ratio for 16 causes of death. Also, the largest smoker mortality ratios are for cancer of the pancreas and cancer of the bladder and not for lung cancer. The lung cancer rate is about 3 times as great for smokers than for nonsmokers, but so are the rates of cancer of the esophagus and of the cervix. On the other hand, chronic rheumatic heart disease, anemia, and cancer of the rectum are reported much less frequently among smokers. In general, a distribution of 16 mortality ratios below unity and 21 above unity out of 37 could easily occur by chance if it were true that smoking has no effect at all on any of the diseases.

It must be emphasized again, however, that the data presented by Dr. Hirayama are in need of careful evaluation. Of the number of problems raised by that study, two are especially vexing.

First, the pattern of high incidence of cancer of the pancreas, bladder, lung, and esophagus raises the suspicion that members of the population have a high incidence of occupational exposure to irritant air pollutants and industrial carcinogens. Indeed, Dr. Hirayama's population appears to have been gathered in districts with a high density of industrial workers. But it is becoming increasingly apparent that the ocupational background of smokers and nonsmokers is of paramount importance in determining the incidence from lung cancer. It is not at all clear what accounts for this interaction between occupational exposure to irritating dusts and fumes and smoking. Selikoff has suggested that there exists a special synergism between smoking and some pollutants.[34] A simpler explanation may be that constant exposure to lung irritants contributes to the cigarette habit so that the more a worker is exposed to irritating pollutants, the more he may smoke.

The second factor impeding critical evaluation of the Japanese data is the dearth of detailed information available about it. We have presented here the most detailed report of results made available by Dr. Hirayama in 1968. Two other reports were made public since then, one in a newsletter published by Seventh-Day Adventists[35] and the other in a news release through the American Cancer Society.[36] Neither one of these two reports offers a detailed picture of the Japanese data. Rather, they report only those diseases for which smokers have a higher incidence that nonsmokers and even here fail to provide the detailed analysis that is required for proper dissemination of results of scientific investigations. Nevertheless, the results as reported[37] were used by the National Clearinghouse for Smoking and Health to prepare follow-up reports to *Smoking and Health*.[33] Since the incomplete results of these later releases are in line with the earlier and much fuller reports in 1968 by Dr. Hirayama to HEW, we have presented those data, even though they are from an older summary of his results.*

If we pull together the information which has become available in the last few years about the prospective studies, we find substantial support for the possibility that the findings linking smoking to lung cancer, and perhaps also to

* It is disturbing to have to evaluate the results of a possibly important investigation from whatever fragments are made available to the public process. Ordinarily little merit would be placed on scientific reports that remain hidden in the files of an agency (as was the case with Dr. Hirayama's 1968 report that was permitted to gather dust in the files of NCSH until this author presented them in 1971 as part of a symposium during the 138th meeting of AAAS in 1971) or are related in newsletters or presented as news releases. Science ought not be conducted behind closed doors and it is to be hoped that a full report of Dr. Hirayama's work will be prepared and properly refereed before publication. Meantime, all attempts by this author have failed to obtain additional information about this important study.

other diseases, were due to a faulty selection process that introduced a large number of biases. A serious disagreement may well exist between a statistical viewpoint—maintaining that if N studies commit the same selection bias, they all may end up with the same erroneous results—and the not insubstantial reasoning that data collected under so many different conditions and yet showing the same results need to be taken seriously. Perhaps it is for this reason that a number of macrostatistical studies (using population aggregates) become increasingly important.

Results of Macrostatistical Population Studies That Conflict with the Relationship between Smoking and Lung Cancer

Contrary to the belief that a large number of observations on populations tend to support the findings that smokers have a higher incidence of lung cancer and other diseases than do nonsmokers, there are many studies using population groupings and aggregates that raise serious questions about that hypothesis. There is no question that the most important of the macrostatistical observations concerns the leveling off of lung cancer mortality, which appears to have started sometime between 1950 and 1960.

Lung Cancer Mortality Appears to Have Leveled Off Starting in 1954

It was suspected in the early 1960s that the prevalence of lung cancer was beginning to level off.[38] Recent findings have verified that lung cancer mortality rates, both in this country and in England and Wales, have stabilized and begun to decline for younger and middle-age population groups. This decline appears to date from 1955 in the United States[5] and from 1954 in England and Wales.[39] The decline in England and Wales is much more marked than that for the United States and apparently started in 1954 for age groups up to 44 years, in 1957 for age groups up to 54 years, and in 1964 for age groups up to 64 years (Figure 3). Clearly, it would be unreasonable to observe a decline in lung cancer rates at a time when the consumption of cigarettes is increasing if it were true that cigarettes are a major cause of lung cancer. The parallel observation of the leveling off and decline of lung cancer in this country and in England ought to have far-reaching negative implications.*

* The harm that may be caused in this entire area by press releases is well demonstrated by the release by Dr. Horn that "it may be three years before final mortality figures for 1970—71 are compiled, but early indications clearly show a lessening of the lung cancer death toll."[40] Dr. Horn then goes on to ascribe the decline in cancer rates to the decline in smoking since 1964. However, the decline in lung cancer rates may date to 15 years earlier.

TABLE 9—Smoking and Each Cause of Deaths, Japanese Data*

	Actual Deaths among Smokers	Expected Deaths†	Ratio of Actual to Expected Deaths
Ca. pancreas	14	0.9	15.56
Ca. bladder	6	0.6	10.00
Ca. lung	40	13.7	2.92
Ca. esophagus	21	8.5	2.47
Ca. cervix	10	4.2	2.38
Other heart disease	22	10.8	2.04
Stomach ulcer	37	21.2	1.74
Rheumatic fever	1	0.6	1.67
Infectious diseases	7	4.2	1.67
Bronchitis	7	4.3	1.63
Ca. breast	3	2.1	1.43
Ca. liver	45	31.9	1.41
Other cancer	39	29.7	1.31
Other hypertensive disease	17	13.5	1.26
Ileus	5	4.2	1.19
Hypertensive heart disease	16	13.6	1.18
Ca. stomach	176	150.6	1.17
Liver cirrhosis	35	31.0	1.13
Other disease	125	110.3	1.13
Other accident	28	26.0	1.08
Arteriosclerotic heart disease	82	76.8	1.07
Ca. tongue	4	4.2	0.95
Senility	37	39.4	0.94
Nephritis and nephrosis	23	26.4	0.87
Diabetes	12	14.3	0.84
Degenerative heart disease	26	34.5	0.75
Syphilis	3	4.2	
Respiratory tuberculosis	38	55.4	0.69
Gastritis, enteritis	9	13.2	0.68
Vascular lesions for central nervous system	387	573.4	0.67
Benign neoplasms	14	21.6	0.65
Pneumonia	23	35.3	0.65
Suicide	20	32.0	0.63
Automobile accident	29	47.5	0.61
Appendicitis	5	8.6	0.58
Ca. rectum	11	26.9	0.41
Anemia	2	4.9	0.41
Chronic rheumatic heart disease	1	5.5	0.18

* Source: Hirayama,[29] Table 5.

† Obtained by applying death rate among nonsmokers for each sex to smokers' population for each sex.

Other Macrostatistical Evidence That Throws Doubt on the Relationship between Smoking and Lung Cancer

There are many much-neglected findings of other macrostatistical studies that conflict with present beliefs about smoking and lung cancer. Briefly, the most striking of these are:

There Are Large Differences in the Geographical Distribution of Both Smoking and Lung Cancer Patterns That Are Completely Unrelated to Each Other

For instance, the highest known lung cancer rates occur in England, Austria, Belgium, and Finland. The United States, Canada, Australia, and New Zealand report a much smaller rate of lung cancer deaths. The lowest lung cancer rates are in such countries as Norway and Italy.[41,42] Yet, per capita smoking rates are, by far, the greatest in Canada, the United States, and New Zealand, considerably lower in England, and lowest in Finland and Austria.[43]

Lung Cancer Mortality for Migrant Populations Falls between the Rates in Country of Origin and New Host Country

This observation has been established predominantly for English immigrants to the U.S., Canada, South Africa, Australia, and New Zealand. It has also been observed for Jewish populations in Israel, the United States, and Canada and for Italian immigrants to the United States.[44-51] For an example of the consistency of the migration effects, see Tables 10 and 11. The observed changes in lung cancer rates of immigrants is of great importance, especially for the U.S., Australia, Canada, and Israel. These are countries with extremely high consumption of cigarettes while England and Italy have a lower per capita consumption. The smoking rates and prevalence of lung cancers among immigrants, when compared to each other and to native-born, often make up a puzzling mixture. For instance, some groups who are the lightest smokers may also report the largest death rate, and vice versa.[53]

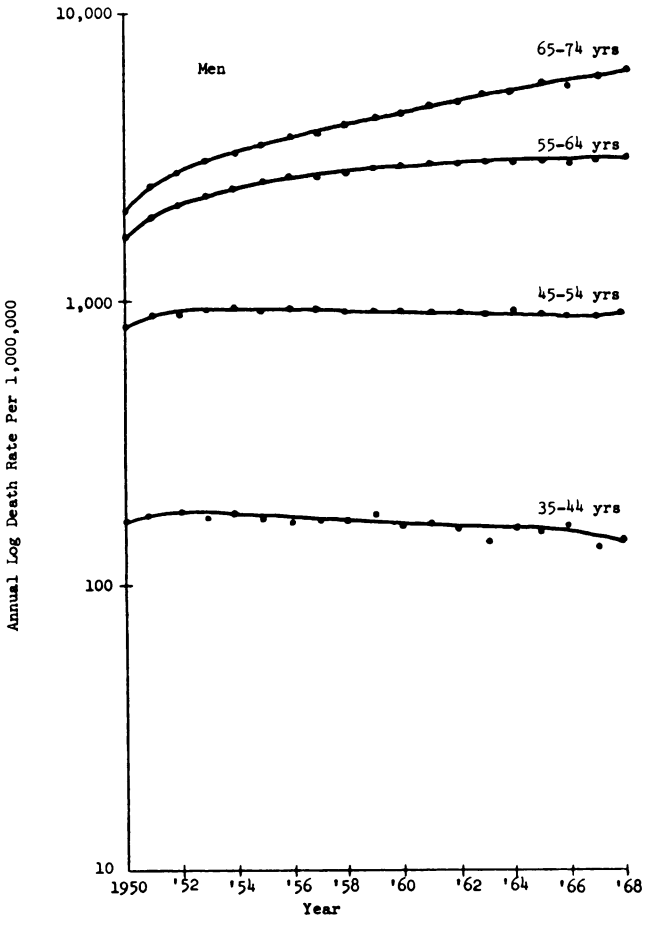

FIGURE 3 Trends in lung cancer mortality reported by Doll for men in England and Wales, 1950 to 1958, by age. Adapted from Doll,[39] Figure 5.

One recent study by Mancuso may be of special relevance. He compared the lung cancer death rates of native Americans who were born and died in Ohio with those of native Americans who were born in a southern state and migrated to Ohio. While the death rates from lung cancer among native Ohio males were somewhat smaller than among U.S. males, the death rates among migrants from the South were considerably higher for white males and approximately double for black males born in the South when compared to black males born in Ohio. Mancuso pointed out that, on one hand, smoking was less frequent among southern males than among northerners, especially for blacks, and on the other hand, that migrants, especially blacks, tended to be employed in the "dirtier" jobs, where they would tend to be exposed to high concentrations of irritants.[53a,53b]

The shift in lung cancer deaths from origin to host rates in the immigrating population suggests the importance of environmental factors in the etiology of this disease. Both Sterling[5] and Stocks[54,55] have suggested that this factor might be the amount of soot-carrying benzpyrene in the atmosphere.

There Are Pronounced Occupational Differences in the Incidence of Lung Cancer

The heaviest incidence is among steel, coke oven, and asbestos workers and most individuals who are exposed to dust or irritating fumes.[34,56-63] Smoking is also very heavy in these groups. It is tantalizing to know what the lung cancer rates in the ACS or U.S. veteran studies would be if these occupational groups were eliminated from an analysis.

There Are Large Numbers of Differences in Lung Cancer Rates for a Variety of Population Parameters

These differences are consistent and occur almost wherever comparisons are made. This is true especially for urban/rural differences.[61,64-67] The constant difference between men and women in the incidence of lung cancer has persisted although the frequency of smoking among women has increased more rapidly than among men. (For instance, in 1950 the male/female mortality ratio was 4.7 to 1, and in 1965 the ratio had increased to 6.1 to 1.[33] A sex differential persists also among nonsmokers.[33]

TABLE 10—Australian Lung Cancer Death Rates (1962–1966) with Comparative Rates for England, Wales, and Scotland (1963)*

Country of Birth and Residence	Rates/100,000 of Population							
	Males				Females			
	40–49 Years	50–59 Years	60–69 Years	70–79 Years	40–49 Years	50–59 Years	60–69 Years	70–79 Years
Native-born Australians	16	60	186	239	4	11	16	26
English and Welsh-born immigrants to Australia	28	125	301	388	7	15	24	45
Native-born English and Welsh	38	173	435	482	10	26	46	51
Scots-born immigrants to Australia	44	157	396	363	5	19	21	55
Native-born Scots	41	208	489	535	34	28	50	85

* Source: McCall and Stenhouse,[49] Table 1.

There Is a Constantly Changing Constellation of Factors Affecting the Lung Cancer Death Rate

One example of such factors is furnished by the interrelated fate of all diseases. Decreases in some must be compensated by concurrent or subsequent increases in others, or vice versa, since the probability of death, unfortunately, remains unity under all conditions.[63,68,69] That a definite relationship exists between the decline in mortality due to respiratory diseases and an increase in lung cancer is only now beginning to be understood.[70,71] It is also interesting to note that wherever attempts are made to simultaneously evaluate the effect of smoking and such other factors as levels of pollution or familial backgrounds, the co-variables have tended to account for much larger portions of the observed variance than has the smoking habit.[54,72,73]

How About the Observation That the Incidence of Lung Cancer Decreases Rapidly for Those Who Stop Smoking?

On close scrutiny, this observation ought to raise serious questions. Individuals who have been exposed to a known carcinogenic agent incur a risk in some relation to the amount of their exposure. Why should the probability of incurring a consequence associated with this risk diminish when an individual is removed from further exposure to a carcinogen? Although it is possible that cessation of smoking calls forth a unique and little understood repair process, a more likely explanation is that the decline in the incidence of lung cancer after "removal" from the smoking habit is yet another manifestation of self-selection.* It is not unlikely that many individuals cease smoking because they are concerned with their health and not necessarily because they are ill. This possibility has been advanced by Doll and Hill (p. 1408 in Reference 27). It is also known that a large number of individuals who stop smoking are actually the light smokers.[74] (To increase the confusion on this issue, doubt has lately been expressed by Doll that the incidence of lung cancer decreases for former smokers when compared to the incidence of the disease in nonsmokers (pp. 152–153 in Reference 75). This conclusion is in line with a recent analysis by Seltzer[76] of mortality data assembled by the Royal Commission.[77] Seltzer points out that the apparent decline in mortality for men who stop smoking may be due to deletion of some of the age groups and follow-up periods from the analysis.)

* Removal from smoking habit may be of degree only, as for individuals who had switched to filter or low tar cigarettes.

TABLE 11—Average Annual Adjusted Death Rate Due to Lung Cancer per 100,000 White Ohio Males*

Population Group	Avg Death Rates (Ages 25–64 and Years 1947–1951)
Native-born white males residing in Ohio	20.85
Immigrants from all foreign countries	
Residing in Ohio	36.67
Residing in Cuyahoga County	38.11
Cuyahoga County residents who immigrated from	
England and Wales	31.75
Italy	18.61
Resident populations of	
England and Wales (1950)	55.48
Italy (1951)	16.26

* Source: Mancuso and Coulter,[52] Table 4.

How About the Dose-Response Curve That Is Often Reported Which Relates the Mortality of Smokers to the Rate of Smoking?

One problem with any dose-response curve is the reliability of the measurements used. Information obtained by questionnaires and household interviews is generally beset with extremely large errors.[78] Differences in the incidence of smoking reported in various studies indicate that such errors exist and that they must be large. But these errors may have disproportionately large effects

because of the relatively small number of heavy smokers. Also, heavy smokers may be especially subject to a variety of "selection" factors, and, in addition, they tend to have characteristics that reflect a person, a state of life, and a mode of behavior which might indicate that the heavy smoker is also an individual who behaves more recklessly with respect to his health than do most of us. He tends to be a heavy drinker,[79,80] overeater (usually inferred from heavier weights of smokers or higher serum cholesterol levels, or both),[81-85] and underexerciser (see especially Table 18 in Reference 9), and is perhaps equally careless about other practices that may detract from his health. It is quite possible that the amount smoked is, in a sense, a measure of his "recklessness."

Finally, it is not always clear that the statement that a dose-response curve exists is justified. Sometimes the zeal of an investigator helps him see a dose-response relationship where none actually exists.[76,86,87]

How About Evidence from Animal Studies?

Kuschner et al.,[88] Leuchtenberger et al.,[89] Shabad,[90] and Stewart[91] reported a number of studies on smoking conducted over a period of years in which cancer-prone animals inhaled cigarette smoke at rates approximating but usually exceeding that of human smokers. The results of all of these studies were negative. A two-part article by Hammond et al.[92] in which they report the production of lung cancer in beagles was, therefore, received as an electrifying announcement by the scientific community. Unfortunately, the report of this experiment has been beset by many extraneous problems.* There has been great discussion about this experiment. Much of the controversy revolves around whether or not slides and photographs submitted by the authors show any abnormalities.[93,96] Another and a most surprising weakness is the failure of the authors to provide a control group. There are no controls included which were subjected to comparable treatment but without exposure to cigarette smoke. Since dust and food particles were free to enter the lungs of the experimental animals along with the cigarette smoke, changes in lung tissue, including cancers, would be expected. There seems to be no question that such particles were allowed to enter since two dogs were reported to have died from asphyxiation caused by entering food particles during and right after smoking experiments and another four died from airborne infections. It is well known that severe changes in the lung epithelium and true cancers result when foreign particles are embedded in lung tissue.[88,97-102] The failure to provide sham smoking experiments is, therefore, almost unprecedented.† The authors pleaded two reasons for having neglected the necessary controls. First, they stated that nonsmoking humans do not "smoke" unlighted cigarettes. Secondly, they pleaded a shortage of technicians.[92] Neither explanation is of great relevance since humans do not inhale smoke and air directly into their lungs through a hole in the trachea. Moreover, it would be preposterous to believe that in such an expensive and crucial experiment not enough money was provided to pay an additional technician to ensure proper controls.

* It started with a well publicized announcement in the press of what had been found, which turned out to be quite different from what was finally reported.[93] Next, the investigators refused to make their slides available for independent review.[94] A manuscript submitted to the *Journal of the American Medical Association* was turned down by a reported 12 reviewers[95] but was then immediately accepted for publication by the *Archives of Environmental Health* by the then-outgoing editor, without requiring the authors to furnish answers to the objections raised.

TABLE 12—Average Age-Adjusted Mortality Rates per 100,000 Males for Years 1959—1967 for Death of Ohio Residents by Place of Birth and Race*

Age-Adjusted (35+)	White	Black
Born and died in Ohio	94.66	85.36
Born in a southern state and died in Ohio	124.95	163.95
Comparable U.S. rates	98.78	136.35

* Source: Mancuso and Sterling.[53a]

Conclusion

It would be very desirable if the antecedent for lung cancer turned out to be or only depended on such a simple event as smoking. The readiness with which the existing evidence has been accepted as demonstrating causality for cigarette smoking perhaps is the best measure for the desire to keep our world simple and orderly. But cancer is a complex disease. New important discoveries of how cancers are produced in animals continue to be reported. The role of many experimental conditions,[2] of common pesticides,[1] or of nitrosamine compounds that have demonstrated high carcinogenic activity and may be produced in significant quantities by the interaction of various common chemical components of our environment[104,105]‡ are but a few

† The results of the experiment are in fact discounted by the recent NAS report on health effects of particulate polycyclic organic matter: "It may therefore be questioned what part of the effect in these experiments can be attributed to smoking and what part to other conditions imposed. Possible factors include the lesser degree of cleanliness of tubing in animals smoking cigarettes without filters and the hypersecretion in the smoking dogs. The sequence might be increased secretion in the smokers, with aspiration leading to infection; pulmonary damage; regenerative changes; and bronchiolo-alveolar tumors" (pp. 178—179 in Reference 7; also see Reference 103).

‡ The recent conference on occupational carcinogenesis to commemorate the 200th anniversary of Sir Percival Pott's monumental observation (March 24—27, 1975) summarizes the many recent discoveries on the relation between industrial and industrially caused exposures and lung cancer. Unfortunately, much of the work disclosed there could not be included in this paper.[105a]

cases in point. But, the evidence for the claim that cigarette smoking causes lung cancer has never been without controversy. Severe criticism has been directed at key studies supporting this contention by some of the world's most prominent statisticians.[31,80,106-113] Unfortunately, medical studies of lung cancer are published in medical journals so that few, if any, of the many studies reporting a link between smoking and disease have ever been published in a principal statistical journal where the methods of sampling and data analysis would have received adequate review. Also, many of the widely circulated summaries, testimonies, commission findings, and even direct reports of experiments have never been subjected to any scientific review whatsoever. Consequently, a synthesis and reassessment of this evidence at the present time would seem to be highly desirable. Since population statistics have contributed significantly to the belief of many that cigarette smoking is a cause of lung cancer, *perhaps we should start by asking how population surveys and statistical studies can contribute to our understanding of the possibly complex causes of lung cancer or, in fact, any cancer?* This question is basic since it includes cigarette smoking as one of the possible antecedents but does not ignore the rich evidence implicating others. If it is true that existing population studies clearly indicate that cigarette smoking is the major cause of lung cancer, then additional large and expensive population surveys to uncover other causes may not be warranted. On the other hand, if this general conclusion is not acceptable, then the groundwork may be laid for a much more inclusive population study.

Bertrand Russell once summarized the essence of scientific review as: "... it is clearly impossible that each of us should verify the facts of geography; but it is important that the opportunity for verification should exist, and that its occasional necessity should be recognized" (p. 620 in Reference 114). In a way, this report is an exercise in geography. It is generally believed that existing evidence has established that smoking is a major cause of lung cancer. This project has undertaken to probe this belief—not to provoke or to please, but to dissect and to analyze. Because we adopt an analytical attitude, it may be difficult to avoid the impression that the focus of this paper is on the critical side. The voluminous research on smoking and lung cancer contains many good as well as bad points. While a critical analysis tends to bring out inadequacies, this should not be taken to imply that none of the past studies are of value. Quite to the contrary—many able investigators have studied this difficult problem with great care and have gathered valuable data, and their analyses have significantly contributed to the understanding of human disease. A critical analysis offers an objective framework for evaluating widely used research methods and analytic procedures but, unfortunately, without singling out individual good or bad points or emphasizing how the work of many of these scientists has enriched our knowledge.

Bearing in mind these limitations, there is yet one other pressing need to closely analyze the statistical studies and population surveys of the effects of smoking. Unfortunately, conventional procedures based largely on animal studies are becoming increasingly inadequate for determining the toxicity of any consumed product or of a widespread pollutant.[115,116] Continuing surveys of human populations may be the major method for monitoring the health of large communities and protecting men from the untoward effects of the byproducts of his many activities. The smoking and health population studies form a model on how such surveys *may* be conducted. If this model is invalid and possibly leads to misleading conclusions, as many respected statisticians and scientists have claimed, then incalculable damage may result in the long run if the shortcomings in this model are not made public.

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AMERICAN COLLEGE OF CHEST PHYSICIANS TO MEET

Over 3000 physicians and allied health professionals are expected to attend the 41st Annual Scientific Assembly of the American College of Chest Physicians. This meeting will take place at the Disneyland Hotel and Anaheim Convention Center, Anaheim, California, October 26 to 30, 1975.

The Chairman of the 1975 Scientific Program Committee is W. Gerald Rainer, MD, associate professor of surgery, University of Colorado Medical Center, Denver. Dr. Rainer and his committee have planned a scientific assembly which will center on the theme, "Clinical Alternatives in Cardiopulmonary Diseases."