A REVIEW OF SOME IMPORTANT PROBLEMS CONCERNING LUNG CANCER

PART I: CONSIDERATIONS OF EPIDEMIOLOGY, ETIOLOGY AND PATHOGENESIS

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BRONCHOGENIC carcinoma remains one of the most challenging diseases faced by the medical profession, not only because of its frequency, but also because so little has been accomplished in its management since the recognition of its increasing significance particularly during the past two decades. Some of the important problems encountered in considering the present situation warrant review.

In previous publications1-2 stress was laid on the importance of early diagnosis, means by which this might be achieved, and the importance of hematogenous spread in determining the eventual outcome. The possibility that emphasis might quite properly be placed on prevention rather than treatment was mentioned in view of the causal association of cigarette smoking. At the present time, all these factors continue to demonstrate a relationship that becomes more firmly established with the passing years and represent fundamental considerations in creating an intelligent attack on this lethal disease.

A. EPIDEMIOLOGY

There is now no longer any question but that the increasing incidence of lung cancer is a real increase demonstrable in age-standardized statistics and not related primarily to improvements in diagnosis and management.3 Cornfield et al.4 quote statistics from Great Britain showing that the lung cancer mortality for both sexes rose from a level of 0.8 per 100,000 population in 1900 to 34 per 100,000 population in 1953 and in more recent years the lung cancer mortality for males in the United States rose from 4 per 100,000 population in 1930 to 24 per 100,000 population in 1951. The Medical Research Council of Great Britain5 reports also that during the decade 1945 to 1955 the death rate from lung cancer increased from 1.8 per 100,000 population to 3.8 per 100,000 population. At the present time the disease, according to these statistics, is responsible in Great Britain for one in every 18 deaths in men and one in every 103 deaths in women. In the most recent textbook dealing with surgical diseases of the chest, Blades6 is able to report that lung cancer accounts in the United States for approximately 10% of all deaths and 20% of the deaths from cancer among males.

B. ETIOLOGY AND PATHOGENESIS

1. Cigarette Smoking

In the epidemiological approach to the elucidation of reasons for increasing frequency of such a disease as bronchogenic carcinoma there are usually five stages in the establishment of a firm hypothesis. In the first instance, a retrospective or historical review is made of patients with bronchogenic carcinoma in order to discover what factors might be common to patients having this disease as elicited on enquiry into their past histories. Once a possible relationship has been suggested by such means, a prospective study is established during which a group of unselected subjects are followed up for a number of years in order to see whether those in which such a relationship exists demonstrate an increasing risk of developing the disease. If both the retrospective and prospective studies establish this relationship, an attempt is made to isolate the agent responsible for the association, and on its isolation efforts are made to remove it from the causative environmental situation. Following its successful removal a test of the thesis is made by a prospective study permitting the population studied to associate with the environmental factor (e.g., cigarettes) once the causative agent has been removed, with an eventual comparison of the results of such a study with that previously recorded when the agent had been present. It is in this light that much of the work on the association of cigarette smoking in lung cancer has been reviewed.

1. RETROSPECTIVE STUDIES

A multitude of studies of this type have now been reported and all demonstrate essentially the same relationship between excessive and prolonged use of cigarettes and increasing risk of lung cancer. One of the earlier reports by Wynder and Graham7 showed that more than 96% of the patients with lung cancer had smoked longer than 20 years and 51% had smoked heavily for more than 20 years. When compared specifically with a control group of patients not having lung cancer but falling into the same age and economic status, the incidence of heavy smoking over such a period fell to 19%. It was rare to find an epidermoid or undifferentiated carcinoma in a male patient who had not been a heavy smoker for years, and indeed there was only an incidence of non-smokers of 1.3% in patients with lung cancer as compared with an incidence of 14.6% of non-smokers in the control group of patients without lung cancer. The verifi-
cation of this association in other retrospective studies warranted the establishment of major prospective analyses of the importance of cigarette smoking.

2. Prospective Studies

Doll and Hill, Hammond and Horn and, most recently, Dorn have produced the three largest prospective studies, and in essence the findings reported are consistent throughout. Commenting on these figures, Cornfield et al. note that the risk of developing lung cancer in cigarette smokers is nine times that of non-smokers and if more than two packs of cigarettes are smoked a day this risk rises to 60 times that of non-smokers. Doll and Hill in studying males over 35 years of age report a lung cancer mortality of seven per 100,000 in non-smokers, rising in those who smoke more than 25 cigarettes a day to 166 per 100,000—a death rate more than 20 times that of the non-smoking members of this study. In between these extremes of smoking the increased mortality showed a progressive increase as the amount of smoking became greater. During this study it became apparent that those who continued to smoke cigarettes while a part of the study, and averaged more than 25 cigarettes a day, showed a lung cancer death rate 40 times that of non-smokers. It is the magnitude of this association that is so impressive. Wynder and Cornfield reported on a study of physicians (who represent a homogeneous economic group with little exposure to industrial irritants and having equal access to diagnostic facilities) in which the lung cancer mortality rate rose from 10 per 100,000 in non-smokers to 133 per 100,000 in smokers averaging more than 35 cigarettes. Socioeconomic factors would not appear to be related to the results of a study dealing with a special group showing such homogeneity.

(a) Study of “Discontinued Smokers”

One of the most interesting observations of these prospective studies refers to the effect of discontinuing cigarette smoking even after a prolonged exposure to cigarette smoke. In view of the stress that had been laid in the retrospective studies on the prolonged, excessive use of cigarettes, it had been initially thought that if one had smoked heavily for longer than 20 years the necessary damage to the bronchial epithelium had already been accomplished and there would, therefore, be no need to suggest that these people should stop smoking. However, in the prospective studies some of the group had given up smoking and were, of course, followed up along with other members of the study. The lung cancer incidence and mortality in these people give factual support for the thesis that there is benefit in giving up smoking regardless of the length of previous exposure. In the Doll and Hill study, those who had given up smoking within the past 10 years showed a fall in the lung cancer mortality rate to 59 per 100,000, and if the smoking had been given up longer than 10 years previously, the incidence fell to 35 per 100,000 population. Cornfield et al. commenting on this observation state that not only is the lung cancer mortality in those who have discontinued smoking less than that amongst those continuing to smoke, but the magnitude of reduction depends on the amount previously smoked and the length of discontinuance, so that this is a progressive change as freedom from exposure permits continuing change in the bronchial epithelium. In a paper given in St. Catharines, Ontario, in September 1958, Alton Ochsner re-emphasized the observation of Hammond and Horn that the incidence of lung cancer mortality in those men who had stopped smoking longer than 10 years previously had fallen to 8.3 per 100,000 per year (“man-years”), approximating that of the non-smoking group in the same study. In this prospective study the age-adjusted lung cancer death rate per 100,000 “man-years” is calculated at a rate of 3.4 in those who had never smoked, and at 8.3 in those “discontinued smokers” of 10 years’ duration when they had smoked less than one pack a day previously (compared with a lung cancer death rate of 57.6 in continuing smokers). The rate was 60.5 when they had smoked one (or more) packs per day previously (compared with 157.1 in those continuing to smoke at the same level). The importance of such observations is self-evident if one thinks that preventive therapy is worthy of emphasis in this disease.

(b) Biological Differences Between “Squamous-Undifferentiated” Carcinoma and Adenocarcinoma

As a by-product of these retrospective and prospective studies there was clarification of the pleomorphic pathological picture of bronchogenic carcinoma, which appears quite definitely now to consist of two different biological and pathological diseases. The “squamous-undifferentiated” type shows a close association through all these studies with cigarette smoking, whereas there is little, if any, association between cigarette smoking and the development of adenocarcinoma. The biological difference in adenocarcinoma was well demonstrated during a symposium on bronchogenic carcinoma in honour of Dr. Evarts Graham at the 85th annual meeting of the American Association for Thoracic Surgery in Boston in May of 1958. During this presentation Burford et al. demonstrated that of 40 cases of resection having five-year survivals only two could be classified as adenocarcinomatous. In the discussion of this paper Ochsner agreed that prognosis was worse in the adenocarcinoma group, in which only 8% of all five-year survivals had this pathological diagnosis. Johnson, Kirby and Blakemore stressed the importance of blood vessel invasion in determining the eventual outcome in resected cases and further stated in the discussion...
that 81% of adenocarcinomata in their series demonstrated blood vessel invasion. In the further discussion of the paper by Johnson, Kirby and Blakemore,\textsuperscript{15} Selye\textsuperscript{17} reported that in every case of carcinoma of the lung with a histological classification of adenocarcinoma, definite blood vessel invasion had been demonstrated in the resected specimens. The lack of any demonstrable association between the incidence of cigarette smoking and that of adenocarcinoma, the poor prognosis after resection in adenocarcinoma, and the extremely high incidence of blood vessel invasion in adenocarcinoma all suggest that this disease is a biological entity and should not be considered in the same light as the "squamous-undifferentiated" group.

This biological differentiation may explain in large part the occurrence of bronchogenic carcinoma in appreciable numbers in women and in non-smokers. Haenszel, Shimkin and Mantel\textsuperscript{18} verified the fact that the use of cigarettes by women predisposes to epidermoid and undifferentiated carcinoma, but not to adenocarcinoma, and demonstrated that the incidence of adenocarcinoma was higher in women. They stressed the fact that a comparison of incidence in male and female smokers would be misleading unless the pathological type was specified, and noted that the supposedly excessive mortality of lung cancer in men virtually disappeared when non-smokers were investigated. In their figures, the lung cancer mortality for female non-smokers varied between 3.3 and 3.9 per 100,000 population whereas that in male abstainers averaged 4.2 per 100,000 population. It was not thought that any hormonal or other sex-linked factor peculiar to lung cancer was necessary to account for this minor difference. Graham\textsuperscript{19} had originally thought that squamous metaplasia and epidermoid neoplasia were attributes of maleness and, therefore, undertook a trial of estrogen treatment of bronchogenic carcinoma in men. This proved to be of no value and shortly thereafter he recognized the importance of cigarette smoking.

Wynder \textit{et al.}\textsuperscript{20} reported 196 cases of carcinoma of the lung occurring in women in which 32% were of epidermoid type demonstrating a marked relationship to smoking habits and 42% were of adenocarcinomatous type with an incidence identical in smokers to that in a control group of non-smokers. They also stressed the fact that the increased hazard of bronchogenic carcinoma in men was not out of keeping with current smoking practices in the two sexes. Women still smoke less than men at all ages above 50 and indeed most women over the age of 50 are non-smokers, whereas half of the women under the age of 50 remain non-smokers. The number who smoke more than a pack a day is infrequent at all ages, even under 40. The length of smoking history may be of importance in the slower increase in lung cancer mortality in women than in men, since it was ex-

(c) \textit{Effect of Inhalation and Relationship to Type of Smoking}

The fact that the risk of cigarette smoking is much greater than that of cigar smoking (and pipe smoking) quite naturally poses the question as to whether differences in inhalation habits offer a rational explanation for this observation. The difficulty in gathering information on this point makes the assessment less factual than might be wished. However, emphasizing this point particularly, Schwartz and Denoix\textsuperscript{22} reported the risk of lung cancer to be greater among those who inhaled than among those who did not inhale. The proportion who inhaled increased with the amount of cigarette smoking, and was greater in those who smoked cigarettes only than in those who smoked pipes as well as cigarettes. Inhalation was many times higher among cigarette smokers than among pipe smokers. In a similar study Hammond\textsuperscript{23} reported essentially the same findings, and Todd\textsuperscript{24} also found that the proportion of cigarette smokers who say they inhale increases with the number of cigarettes smoked per day and decreases with advancing years. Hammond\textsuperscript{25} suggests that the fact that cigarette smoke is alkaline, stronger and often capable of inducing nausea affords a ready explanation of this difference.

At the present time, therefore, it would appear that the habit of inhalation offers an adequate explanation of the different lung cancer mortality ratios between cigar smokers (1.22), pipe smokers (1.12), cigarette and pipe or cigar smokers (1.43) and cigarette smokers (1.68). These figures are expressed on a basis of a ratio of 1.00 for non-smokers.\textsuperscript{9}

3. \textit{Isolation of Carcinogenic Agent}

Pathological evidence to support the thesis that a carcinogenic agent is present in cigarette smoke has been demonstrated by direct and indirect methods and by experimental studies.
(a) Changes Induced in Bronchial Epithelium by Exposure to Cigarette Smoke

In the first place, Black and Ackerman\textsuperscript{26} stressed the frequent association of the triad of bronchial epithelial changes characterized by squamous metaplasia, carcinoma \textit{in situ}, and invasive epidermoid or undifferentiated carcinoma of the lung. It was suggested that the initial response of the bronchial epithelium to irritation was a progressive metaplasia with cellular hyperactivity in the basal layers and that the change subsequently to a carcinoma \textit{in situ} almost invariably indicated the nearby presence of an invasive tumour. It was important to note that these findings were not present in patients with adenocarcinoma.

Auerback,\textsuperscript{28} reporting on these changes at a symposium on Cancer of the Lung held during the 3rd National Cancer Conference, Detroit, in 1956, indicated that application of carcinogens produced epithelial changes prior to malignant degeneration of the bronchial epithelium and at multiple sites. He postulated that if an environmental exogenous agent in cigarettes was responsible for this change one should find epithelial changes in patients dying of other causes, if they had an adverse smoking history. Consequently, he analyzed the epithelial changes in both smokers and non-smokers, describing for the first time the high incidence of basal cell hyperplasia which progressed to stratification, squamous metaplasia and finally carcinoma \textit{in situ}. The advanced stages of this sequence were encountered almost as frequently in the heavy smokers dying of other causes (98.0\%) as in those dying of lung cancer (99.8\%), and were much less frequently seen in non-smokers (16.8\%). There was a remarkable parallelism between the smoking habit and the incidence of these changes. The proportion of sections with carcinoma \textit{in situ}, a lesion never found in non-smokers, rose from 0.3\% in men smoking less than ½ pack of cigarettes per day to 11.4\% if two or more packs were smoked daily.\textsuperscript{27} The widespread distribution of the lesions was fully described in an early report\textsuperscript{28} by this same group and thought to offer, in part, an explanation for the discouragingly low cure rate encountered after resection of primary disease.

Squamous metaplasia of the bronchial epithelium had been the first abnormality in the tracheobronchial tree to attract attention as long ago as 1919, during which period it seemed to be associated with inflammatory diseases such as influenza and bronchiectasis, but Hamilton \textit{et al.}\textsuperscript{29} undertaking an evaluation of this problem in Canada, demonstrated a significant difference in the incidence of basal cell hyperplasia in cases of carcinoma of the lung—and in smokers—which could not be explained on the basis of inflammation alone.

Commenting further on these changes, Auerback \textit{et al.}\textsuperscript{30} felt that the lesions occurring in the bronchial epithelium of non-smokers who died of causes other than lung cancer, although infrequent and less advanced, warranted study. Three possible causes were postulated: (1) infections, (2) exposure to air contaminants, and (3) the effects of ageing. A study of children under 15 years of age was therefore established and, perhaps surprisingly, the changes in the bronchial epithelium were similar to those in the non-smoking adults previously analyzed, with some epithelial change present in 16.6\% (cf. 16.8\%) and no evidence of carcinoma \textit{in situ}. The ageing process would seem therefore to be of little significance, nor did the findings provide any support for the thesis that pneumonia would produce residual epithelial changes, although the majority of lesions in children appeared to be the result of the repair of ulcers which could conceivably result from unidentified respiratory infections. Because of the high degree of association between ulceration and the occurrence of epithelial lesions characterized by the absence of cilia it was felt that inhaled irritants played a role in the production of epithelial changes in only a very few of these children.

(b) Significance of Squamous Metaplasia

It has long been known that bronchial epithelial changes progressing, as the result of repetitive insult, to squamous metaplasia may be reversible once the insult is withdrawn, but the presence of these areas in which ciliated epithelium is lacking may have more fundamental significance, since the slowing in the stream of mucus which contains an inhaled and potentially carcinogenic agent may thereby permit it to act on a local area of epithelium for a sufficient length of time to induce the permanent changes of frankly invasive carcinoma.

Macklin\textsuperscript{31} stressed the importance of delay in the passage of mucus when he described the sequence of events following inhalation of an environmental agent such as cigarette smoke. In this pathological sequence the diffusible products of cigarette smoke are absorbed to provide the patient with the "lift" he receives from smoking while the tiny ultramicroscopic particles are trapped in the alveolar mucoid fluid where they are picked up by alveolar phagocytes (pneumonocytes) to produce "dust cells" which fall into the same category as "heart failure cells". These "dust cells" disintegrate on their ascent to the glottic area, releasing their contents which are borne along on the moving carpet of mucus carried by the vital escalators of the ciliary fingers. The mucus converges and lingers in the hilar area where there is, therefore, concentration and stagnation of carcinogens. The fact that potential carcinogens are not merely puffed in and out of the lung in the visible vapour trails but are actually retained in the lung following inhalation has been verified by Wynder and Hoffman,\textsuperscript{32} who demonstrated that fluorescent material, containing the hydrocarbons which represent the potential carcinogens, was in large part retained in the lung on inhalation and not expelled promptly in the next breath. Pursuing this
thesis still further, Hilding demonstrated that carcinoma of the bronchial tree was prone to occur at the root of the lung where there are large obstructing openings from the tributary bronchi which result in slowing of the stream of outdrifting mucus and where squamous islands are apt to occur which similarly delay the passage of the mucus. These changes permit carcinogenesis where the mucosal blanket is consequently retarded. By reversing tracheal grafts in dogs and chickens Correll and Beattie were able to demonstrate that when recovery occurred and cilia began to beat distally in the reversed graft there was accumulation of mucus at the distal anastomosis, creating a static area, cleared only by coughing or aspiration. They postulated that carcinogens might accumulate at such areas in experimental animals and are investigating the possibility that neoplasms may be produced by inhaled carcinogens concentrated in this fashion at specific sites of mucosal stasis.

(c) Demonstration of Carcinogenic Agent in Cigarette Smoke

Species and strain specificity have made it difficult to isolate the exact carcinogenic agent in cigarette smoke. However, the experiments of Wynder, Graham and Croninger established without doubt the fact that condensed cigarette tar does contain a carcinogenic agent, and merely because the lungs of mice and other experimental animals represent sites in which it is difficult to produce lesions is not an adequate reason biologically to ignore this factual demonstration of carcinogenic activity. Leuchtenberger et al. demonstrated over successfully demonstrated an increase in hyperplasia, metaplasia, dysplasia and carcinoma in situ in the lungs of mice exposed to cigarette smoke for a relatively short period of time. It is interesting to note that these changes were of the same type as the bronchial epithelial changes previously described by Auerback in human lungs exposed to cigarette smoking. The species variation in biological resistance to carcinogenesis is well illustrated by the experiments of Rockey et al. who applied tobacco tar directly to the tracheobronchial epithelium through a permanent tracheal window in dogs. The application was made through a bronchoscope, and squamous metaplasia of the treated epithelium occurred rapidly. In the original report it was noted that up to 11 months there had been no further progression of these lesions to frank invasive carcinoma despite the fact that the initial response had resembled that encountered in humans. Subsequently, however, Carr was able to report a personal communication from Rockey in which the eventual production of invasive carcinoma in these experiments was noted.

The long period of insult necessary prior to the successful demonstration of frank carcinogenesis is of course in keeping with the natural history of similar disease in humans.

4. Elimination of Carcinogenic Agent

Since the actual agent in the cigarette tar has not been isolated, the present attack on this problem must be directed at removal of the major carcinogens in the cigarette tar which appear to be contained in the carbon tetrachloride fraction of the neutral tar. As Wynder points out, experimental dose-response studies are of great practical significance in that they show that if the tar exposure is reduced below a certain point the rate of tumour formation, at least in the experimental animal, is significantly reduced. In this respect these observations are similar to those of the epidemiological studies quoted above which show the same relationship. It therefore becomes of obvious practical importance to determine ways by which the tar content of the tobacco smoke condensate can be reduced.

(a) Reduction of Carcinogens in Cigarette Smoke

Practical methods of accomplishing this purpose at the present time include the use of tobacco which may have a relatively low tar content, the provision of a porous paper (which allows a larger proportion of air to come through the paper, diluting the smoke and thus reducing the amount of tar per puff), and, of course, the use of filters. Filters, it must be stressed, serve only one single purpose in reducing the total amount of tar in the smoke. They have no specificity in removing selective portions of the tobacco tar. Nonetheless, by attempting to observe these necessities it has been possible in some cigarettes to produce a 30 to 50% reduction in the tar content of the cigarette vapours. In Canada, for instance, according to the January 1960 issue of Consumer Reports the average amount of tar found in the smoke per single cigarette has reached a level of 21 mg. for a regular filter cigarette as compared to 27 mg. in December 1958, 29 mg. for a king-sized filter cigarette as compared to 35 mg. in December 1958, and 42 mg. for a king-sized cigarette without a filter, as compared to 46 mg. in December 1958. In the overall picture there was a variation from 10 mg. per cigarette to 47 mg. per cigarette.

The efficiency of a filter will, of course, be predicated on the resistance it offers to the passage of tobacco tar, but if made too resistant, the effort of drawing smoke through the filter will be so great that it will destroy the pleasure of smoking. Similarly, if the type of tobacco yields a level of cigarette tar below 10 to 15 mg. per cigarette, the flavour and aroma are reduced to a point where the pleasurable sensation achieved by smoking is diminished. Therefore, there would appear to be an

*Addendum: Bronchogenic carcinoma has been produced in the dog at the distal anastomosis following the instillation of a benzanthrene derivative. (E. J. Beattie, M.D., Personal communication, February 18, 1961.)
inescapable minimum level to which such measures can be carried at the present time.

(b) Projected Methods of Reducing Carcinogens in Cigarette Smoke

In the future, investigation will include a study of the value of temperature reducants during the combustion process, since the formation of carcinogens is related to the burning temperature and not to the presence or absence of oxygen. When the temperature is reduced below 700° C., the biological activity is greatly reduced as compared with that at the usual burning temperature of around 888° C. Modification of these temperature levels, if achieved, could therefore influence the carcinogenic activity of cigarette smoke. In addition, since the higher polynuclear substances are the major carcinogenic components, studies are indicated in attempts to induce modification of pyrolysis by the use of a variety of catalysts in order to determine whether the polynuclear content of tobacco smoke condensate can be reduced. At the present time, no practical application of these theoretical possibilities has been achieved.

(c) Importance of Cigarette “Butt-Length”

The methods by which these higher polynuclear substances are formed during the combustion of cigarette tobacco has led indirectly to further statistical support for the thesis that cigarette smoking is an important factor in the pathogenesis of bronchogenic carcinoma. It has been shown that cigarette tobacco, when burned, is condensed and redistilled at a more proximal part of the cigarette, there to be subjected to further combustion, condensation and redistillation, with a sequential repetition of the process until the carcinogenic agents become highly concentrated in the butt portion of the cigarette. The butt, therefore, becomes the most dangerous part of the cigarette and this process probably explains quite satisfactorily the few exceptions to the high degree of correlation between the age-standardized lung cancer death rates in various countries and the per capita consumption of cigarettes in those countries several decades previously. Doll et al.11 point out that the United States has a relatively high cigarette consumption but a comparatively low incidence of cancer of the lung as compared with Great Britain (e.g. 202 for men on the basis of 1296 cigarettes smoked as compared with a rate of 461 for men in England and Wales on the basis of 1378 cigarettes consumed annually). In attempting to rationalize this finding Doll and his group demonstrated that the average length of United States butts was 30.9 mm. or 65% greater than the British average of 18.7 mm. More striking still was the fact that two out of every three British butts were less than 20 mm. in length whereas fewer than one in 10 of the American butts were smoked down to this level. At the other end of the scale only one in approximately 40 of the British butts was 30 mm. or longer, while as many as half the American ends were discarded at this length. In both countries the filter-tipped butts did not differ greatly from cigarettes without filter tips, but only 13% of the English butts were filter-tipped compared with 60% of the American sample. Since quite a small difference in butt length might readily result in a substantial difference in the amount of carcinogen inspired, it was thought that this finding could explain the relative difference in incidence in the two countries. Hammond and Wynder12 report the average butt length in Canada to be 27.9 mm., only slightly less than the mean length of the United States sample.

It has been known for a long time that the incidence of lung cancer tends to be higher amongst the poor than in the “upper classes”. Cohort63 reported this increase to be 40% in New Haven. Dorn and Cutler,41 studying 10 metropolitan areas in the United States, also found a consistent increase in the incidence rate of lung cancer with decreasing socioeconomic class as indicated by income. In the Canadian study Hammond and Wynder12 reported the mean length of the cigarette butts to be greater for those collected from the upper socioeconomic classes, intermediate for those collected from the middle classes, and least for those collected from the lower classes. Of butts collected from the upper classes 59.4% had filter tips while only 44.4% had filter tips in those collected from the lower classes. It was felt that these differences in average butt length, therefore, might well account for the reported differences in lung cancer death rates in various countries and various socioeconomic classes. It would not appear to be necessary (as Cohort63 originally suggested) that other environmental factors should be suspect. As suggested by Consumer Reports,41 quoted above, the average amount of tobacco consumed per cigarette appeared in this latter study also to be roughly proportional to the original length of the cigarette.

5. Public Education with Regard to Hazards of Cigarette Smoking

Since it has been impossible as yet to isolate and eliminate the exact agent responsible for this association of cigarette smoking and lung cancer, it is not possible as yet to provide definitive proof of the association by undertaking a further prospective study of smoking once the agent has been removed, thus completing the epidemiological assessment of the association. However, analysis of valid statistical information has resulted in tremendous increases in our knowledge of this association since the highly emotional publication by Henry Ford (following his talks with Thomas Edison) in 1914 entitled “The Case Against the Little White Slaver”.45 Statistics such as those summarized above led a study group of the National Cancer Institute, the National Heart Institute, the American Cancer
Society and the American Heart Association to arrive in 1957 at the following conclusion: “The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung.” In the same year, the British Medical Research Council agreed that cigarette smoking was a major cause of lung cancer. The National Cancer Institute of Canada in two reports in 1958 concluded also that, although it was not established that cigarettes “caused” lung cancer, cigarette smokers have a greater risk of dying of lung cancer than non-smokers and the risk increases with the amount smoked.

If these facts can be accepted, as the present author believes, then certain conclusions can be drawn concerning proper medical advice on the problem:

1. The habit of cigarette smoking should be discouraged, and emphasis should be placed upon the evidence that the lung cancer mortality in “discontinued smokers” tends to fall progressively towards the base-line of lung cancer mortality in non-smokers. In other words, it is never too late to stop smoking.

2. If the public is to continue smoking they should, as intelligently as possible, check the tar yield of the cigarettes consumed, use regular-length cigarettes with filters, and discard them when smoked no more than half their length.

Education of the public concerning these hazards must be continued, but there is some question as to the emphasis that should be placed on the various age groups. Undoubtedly, as Barry stresses, there are deep-seated psychological impulses related to the whole concept of orality which tend to perpetuate the smoking habit. Nonetheless, in a survey by Snegireff and Lombard in 1959 expressing the result of a survey of physicians during an initial five-year period between 1954 and 1959 it was discovered that the percentage of non-smokers had increased from 34.1% to 44.5% and that those who smoked more than a pack a day had shown a decrease from 30.4% to 18%, indicating that one group of the adult population, at least, is capable of altering underlying smoking habits. In the past it has been suggested that adolescent education is essential in this regard, although admittedly difficult when faced with the need to counterbalance the effect of advertising. A recent report by a study group of the Public Health Department of the London School of Hygiene and Tropical Medicine demonstrated that a high percentage of children are smoking at the age of 11 years and that 80% of boys become regular smokers within two years of starting smoking. Because of the emotional factors involved in tobacco habituation during adolescence, related to tribal experience, assertion of individuality, and rebellion and defiance of authority, it may well be that initial attempts at educational persuasion in this age group will provide a very low yield of success. Since these factors are not so prevalent amongst adults, one might reasonably assume that the educational attack should be directed at the older age groups first, particularly since children coming from non-smoking families smoke much less than those from families in which cigarette smoking is customary. This group of children, if coming in increasing numbers from an increasing number of non-smoking families, might theoretically be expected to create an appreciable volume of example for other adolescents in their own groups, and a progressive impetus may thereby be achieved in the increase in the size of the non-smoking public of all ages.

Nonetheless it is disappointing to consider the apparent lack of effect of current educational attempts. Hammond and Percy, in a study of “ex-smokers” are forced to conclude that only 6.3% gave up the habit because of reports linking smoking to lung cancer while 2.4% stopped because of reports that smoking had a bad effect on health in general. In other words, only 1.6% of men with a history of regular cigarette smoking gave up the habit because of reports relating cigarettes to either lung cancer or other diseases. Usually smoking was discontinued because some condition such as coughing was made worse by the habit.

OTHER RESPIRATORY EFFECTS OF CIGARETTE SMOKING

The fact that tobacco smoking may be associated with other respiratory disease has also received some support in recent years and this fact accentuates the importance of cigarette smoking in relation to respiratory complaints of all types. Higgins demonstrated a clear association of smoking with persistent cough and sputum and showed a marked trend to increasing degrees of these complaints with increasing tobacco consumption. There was an increase in the incidence of “chronic bronchitis” (defined as persistent sputum and at least one chest illness in the past three years) and in general more chest illness, wheezing and dyspnea amongst smokers as compared with non-smokers. In direct measurement the maximum breathing capacity was found to be nine litres less in smokers than in non-smokers of the same grouping. Blackburn, Brozek and Taylor also demonstrated that the vital capacity was smaller, the residual volume larger, and the ratio of residual volume to total lung capacity greater in smokers. These findings were those which might be expected to result from a functional increase in airway resistance. It is important to note that this report stressed the fact that in the group which had successfully stopped all smoking the lung compartment values were similar to those of the group which had never smoked. Flick and Paton verified this relationship between the maximum expiratory flow rate and smoking. They suggested that smoking might initiate a definite sequence of events leading to the production of emphysema. It was felt that the in-
halation produced epithelial changes with loss of cilia going on to bronchitis with terminal bronchiolitis which led to alveolar obstruction and progressive distension and rupture of alveoli with loss of elasticity. Following this, fibrosis developed with alveolar and bronchial infection and the characteristic end stage of emphysema. These findings are in keeping with those quoted by Ochsner\(^4\) when he stated that the death rates due to a combination of cancer of the lung and bronchitis and emphysema in the United States have now passed those of heart disease. It was Ochsner's contention that both these changes were related to the cigarette smoking habit.

Such relationships merely strengthen the sense of urgency in the need for proper public education in the lung cancer problem.

**Discussion of Other Possible “Causative” Factors**

The objection to the ready acceptance of the important relationship of cigarette smoking and lung cancer incidence is largely based on theoretical statistical objections to acceptance of unqualified conclusions from a clinical study which does not procure or process ideal statistical data. The possibility of bias in sampling and the suggestion that the groups selected are not representative samples of the general population have both been considered in these objections. It is also suggested that the demonstrated association between lung cancer mortality and smoking might not be a direct relationship but rather one dependent upon a third and yet unrecognized factor.

Berkson has underwritten much of this statistical discussion in a series of recent papers.\(^5\)\(^-\)\(^6\) In essence his explanation of the association includes three possible and somewhat theoretical factors which might invalidate definite conclusions from the data obtained. In the first place, the association might be the result of a spurious statistical phenomenon, since the smoking history obtained is subject to wide variation, the validity of death certification (on which such studies are based) is doubtful, and the samples of the reference population are not large enough. The accumulated volume of present evidence, all uniformly consistent in results, argues effectively against this supposition.

In the second place, the association might be on a constitutional basis in the sense that smokers differ constitutionally from non-smokers. To enlarge upon this presumption that the disposition not to smoke is a reflection of constitution, there may not only be constitutional factors involved but, as noted above, deep-seated psychological urges, as regards the whole concept of orality. It is, of course, recognized that there are certain characteristics of smokers in general which differ from those of non-smokers. For example, they consume more alcohol and black coffee, they change jobs more frequently, they engage more in athletics and it is said that they are more likely to have one parent with high blood pressure or coronary disease.\(^4\) To put this on a slightly more factual basis, Fisher has suggested that there may be a genetic element to this constitutional difference between smokers and non-smokers. In an initial report in 1955\(^6\) and again as a part of a general discussion of the cancer controversy on smoking in 1959,\(^6\) he notes that only 12 of 51 monozygotic twins differed in their smoking habits whereas 16 of 31 dizygotic twins differed in smoking habits. In the first case, less than one-quarter of the group showed this difference whereas in the second case more than half of the group demonstrated a significant difference in habituation to smoking.

These are, of course, important considerations because undoubtedly the biological resistance to invasive cancer is now a fundamental part of intelligent thought about cancer production. A resistant individual may, for instance, smoke heavily all his life and never run an appreciable risk of developing an invasive neoplastic disease. On the other hand, no report has as yet appeared which suggests that those who have stopped smoking, after once having become habituated, run any risk of developing other serious physical or mental diseases as a result of the constitutional or psychological change that follows cessation of exposure to cigarette smoke. This alternative would appear to be one of considerably greater predictable safety. Unfortunately, apart from a careful study of past family histories to indicate both longevity and freedom from cancer at all sites in both maternal and paternal strains, there is no way at the moment of illustrating biological resistance in any individual patient. Therefore, it would be unwise to stress this possibility of constitutional or genetic safety until it can be demonstrated more objectively.

In the third place, and on a highly theoretical plane, Berkson has chosen to postulate that it may not be the constitutional factor which determines the tendency to cigarette smoking but that smoking itself may increase the "rate of living" or in other words alter the internal environment of the body cells modifying these biological processes as they affect the ageing of tissues. He suggests that in diseases having a pronounced gradient with age, such as cancer and heart disease, the general death rate among smokers is similar to that among non-smokers of a more advanced age. In general, this would appear to be a less attractive hypothesis than that suggesting that constitutional difference is the more fundamental factor.

The mere fact, of course, that the lung cancer mortality rate in "discontinued smokers" falls progressively to approach that of the non-smoking public as time goes on, demonstrates the fact that the constitutional factor, although perhaps capable of protecting people from carcinoma when the host harbours adequate constitutional resistance, is not alone capable of producing the changes that will go on to bronchogenic carcinoma without the ad-
ditional insult of a precipitating "cause" in a patient sensitive to invasive cancer in general.

Implication of Other Environmental Factors

There is no question but that the personal aspects of the general unwillingness to accept cigarettes as a "cause" of lung cancer have been supplemented by the undoubted association, to a lesser degree, of other environmental factors which may play a role in the inception of the disease in some instances.

1. Industrial Hazards

There is a statistical basis for suspecting carcinogenic atmospheric pollutants in the following industries in which the risk of lung cancer exceeds that of the general population. These have been well documented by Huerper.63, 64

1. Radioactive dust as in uranium mining and refining.
2. Asphalt dust as in asphalt pitch, soil and on roads.
4. Tar fumes from tar manufacturing and coke-oven servicing.
5. Asbestos from asbestos mining, processing and weaving.
6. Arsenic from arsenic mining, smelting and in pesticides.
7. Nickel carbonyl in nickel ore refining and buffing.
8. Chromates from chrome ore smelting, plating and in pigments, paints, inks and abrasives.

It was originally thought that there was an appreciable hazard to employees in the railroad industry exposed to diesel fumes, but a recent paper by Kaplan66 suggests that there may be no true relationship between diesel engine exhaust fumes and primary lung cancer.

In the overall picture there would be no reason-able doubt that these specific industrial exposures are hazardous and contribute to the development of pulmonary cancer but against the broad picture of the great volume of material affected, such exposure accounts for only a minute portion of the increased incidence of this disease.

2. Atmospheric Pollution

Although specific industrial exposure may be relatively unimportant in the overall picture, general atmospheric pollution in large urban areas does undoubtedly represent a very real and signifi-cant hazard to the public. It is in the assessment of the magnitude of this hazard that arguments have arisen in the past. Huerper63, 64 originally felt that the greater significance of cigarette smoking was largely unproven. He quoted the lack of a consistent relationship between the consumption of tobacco in different countries and the incidence of lung cancer, but, as noted above, this may be adequately explained by the smoking habits in the different countries. His emphasis on the fact that lung cancer incidence was noted to increase early in the present century, before a major increase in the use of cigarettes, is valid only if cigarettes are considered to be the only cause of lung cancer and this is, of course, not a proper postulate. Indeed the major increase in lung cancer mortality is associated with the acceleration in the use of cigarettes following the first Great War and the magnitude of this association remains now un-challenged.

Fisher62 also estimated the increased incidence to be greater in men than in women, although he believed that women were increasing their smoking habits more rapidly than men. However, Cornfield et al.4 are able to quote figures to indicate that the male per capita consumption of cigarette tobacco increased during the period 1906 to 1956 relatively greater than did the female per capita consumption during this same period and, therefore, this constitutes in fact one of the links in the chain of evidence implicating cigarettes.

One is left, therefore, with the evidence that the incidence of and mortality from lung cancer are greater in urban than in rural areas. Certain fundamental considerations appear important in assessing the relative importance of this observation. For instance, it has been recognized in experimental carcinogenesis for many years that externally applied carcinogens exhibit a cumulative effect and it would seem reasonable to assume that epithelial surfaces exposed to external irritants will react in similar fashion. In the human host there is no question but that the skin and epithelium of the respiratory tract are treated very poorly by the environment, being subject to repeated and varying insults, and it is interesting to note that the reaction of these two epithelial surfaces to such repetitive trauma is very similar, with squamous metaplasia a fundamental attribute of the reaction of the bronchial epithelium and hyperkeratoses the response of the epidermis. Rather, therefore, than attempting to implicate one agent or another, it is more reasonable to assume that potential carci-nogens reaching the epithelial lining of the tracheo-bronchial tree will exhibit a cumulative effect similar to that demonstrated in experimental external carcinogenesis.

In Rockey's studies67 it was possible to demon-strate the progressive effect of painting tobacco tars on this surface, and Kotin, Falk and McCammon68 have reported a similar response using atmospheric pollutants. In their experiment using an inbred strain of mice they exposed one group to an atmosphere of ozonized gasoline and a control group to an atmosphere of washed air, over a period of 92 weeks. In the first group the incidence of hyperplastic and metaplastic changes in the epithelium was encountered more frequently and pulmonary tumours (adenomata) appeared in
9.6% as compared with an incidence of 1.6% in the control group.

Clinical support for such an assumption of cumulative association has been provided by the papers of Mills and Porter. In 1957 they reported that a person who smoked 16 to 35 cigarettes a day ran a risk of developing lung cancer that increased by four to six times. In another group who drove annually more than 12,000 miles in heavy downtown traffic the risk of developing lung cancer increased two to three times, and in people who lived in polluted downtown areas the risk of lung cancer increased two times. If one included a combination of these three variants, as in a cigarette smoking cab driver who lived downtown, then the risk of developing lung cancer increased by 40 to 120 times. In 1969, analyzing the same data, they demonstrated, as far as driving was concerned, that the hazard was greatest at all ages over 40 when the drivers were residents of polluted areas and that less hazard was encountered in those who lived in suburban regions. The hazard was completely absent when driving was restricted to open country roads. In general, driving 12,000 miles annually in urban traffic produced twice the risk of country driving. They suggested that motor exhaust gases were a dominant factor in the increase in the ozone-type smog which became an appreciable health hazard if the ozone concentration exceeded 0.1 part per million.

However, this cumulative association must not colour one's appreciation of the fact that the magnitude of association between lung cancer and cigarettes is far greater than that for any other association in environmental influences. The reports of Mills and Porter are in agreement with the Hammond-Horn studies quoted previously, which demonstrated a markedly higher death rate for bronchogenic carcinoma among smokers, whether they lived in cities or in rural areas. More recently Hillis and Cameron have studied the incidence of bronchial carcinoma in rural areas, comparing the tobacco consumption of smokers in town and country using urban and rural hospital populations, urban and rural mass radiography, and tobacco consumption in urban and rural patients with lung cancer as a basis for a statistical comparison. Smoking histories in urban and rural areas were surprisingly consistent and in the rural patients studied with bronchial carcinoma the percentage of smokers was as high, and the amount of tobacco consumed at least as great as in large urban series. The histological types of carcinoma thought to be related to smoking were found in the same proportion as in towns and the relative distribution of squamous carcinoma, undifferentiated carcinoma and adenocarcinoma was similar to that in several urban series. The clinical pattern of bronchial carcinoma was identical to that observed in towns. It was concluded that the relationship between smoking and bronchial cancer seemed to hold in the country as it did in the town, despite the fact that these rural patients were exposed to negligible or minimal air pollution and not to any other known hazard.

The falling hazard in "discontinued smokers", referred to above, of course supports the fundamental importance of the association of cigarette smoking and lung cancer. Interesting support for this contention comes from the study of Wynder and Lemon, who reported on admissions to eight Seventh Day Adventist Hospitals in California in which the majority of the patients lived in smog-polluted areas. Both Seventh Day Adventists (who refrained from smoking and alcohol) as well as persons of other religious denominations were admitted to these hospitals. Over the period studied there were 118 cases of lung cancer in non-SDA males whereas only one case of lung cancer was seen in the SDA males although 12.4 cases would have been anticipated if a similar percentage had been affected. The incidence rates for lung cancer, oral cancer, esophageal cancer and laryngeal cancer were similar in SDA males and females. On the assumption that exposure to atmospheric pollution was similar in these groups, the association between cigarettes and lung cancer appeared inescapable.

The importance of atmospheric pollution should not be minimized, however. An interesting survey recently reported by Dean concerning the incidence of lung cancer amongst white South Africans warrants note. He states that white male South Africans have long been the heaviest cigarette smokers in the world, yet they demonstrate a relatively low lung cancer mortality rate. No attempt is made in this study, of course, to analyze the butt length of discarded cigarettes, which might explain this observation as it has done in the case of the difference in mortality in Great Britain and the United States. Nonetheless, there was a rapidly increasing incidence of lung cancer in the growing cities and a high incidence in the younger age group of immigrants from Britain, suggesting that smoke, smog, traffic fumes, etc., were important factors in this increase. Until the importance of the butt length has been assessed in this regard, however, one should not accept these figures without some qualification. The fact that the excess lung cancer mortality amongst British male immigrants as compared to Union-born white men was found only in those dying of lung cancer under the age of 65 suggested that the greater liability of the more recent British immigrants was a relatively new phenomenon and probably due to exposure to etiological factors before they left Britain. This might, of course, be due in some part to industrial or atmospheric pollutants but habits of smoking established in Great Britain would probably carry over into the new country where these immigrants might well smoke their cigarettes to a much shorter butt length than do native-born white males.
**RELATIONSHIP BETWEEN CIGARETTE SMOKING AND OTHER DISEASES**

It is not proposed to evaluate the association of cigarette smoking and diseases other than those of the tracheobronchial tree. However, much has been made statistically of the increased death rate from other causes in patients who are cigarette smokers, since it was felt that it would be difficult to understand how cigarette smoking could be pathologically related to a variety of quite dissimilar diseases. Nonetheless, in a discussion of these matters one must emphasize that it is the magnitude of the association between cigarette smoking and lung cancer that is the important factor, since none of the other diseases demonstrate such a tremendously increased incidence in cigarette smokers. In these other diseases it is quite apparent that a third factor may be relatively more important and that the use of cigarettes may merely represent a situation which aggravates the underlying pathological state. The incidence of coronary artery disease and myocardial infarction, for instance, is very great in non-smokers (as well as in smokers) as distinct from the low incidence of lung cancer in the non-smoking group. Therefore, the association of cigarette smoking is less important in this respect, despite the fact that repeated surveys show that cigarette smokers do have an increased incidence of these diseases. Many agents are present in the cigarette smoke which is inhaled and it is not necessarily the tar products which are associated with other diseases.

Scott\(^7\) suggested that cigarettes increase the blood pressure by 10 mm. at the diastolic level and 15 mm. at the systolic level and also produce a pulse rate elevation of 18 per minute. These changes disappear when the cigarette is finished. In addition, limb volumes decrease and skin temperature is lowered during smoking, indicating arteriolar narrowing. The occurrence of such changes has been further documented recently by McDevitte and Wright\(^8\) who record the acute effect of smoking in producing constriction of the peripheral blood vessels, an increase in blood pressure and an increase in pulse rate. These factors, although not initiating the essential pathological change of coronary artery disease or peripheral vascular disease, may well aggravate these conditions and this aggravation in some part explains the association statistically. In this regard it is interesting to note that the incidence of coronary artery disease and myocardial infarction was similar in Wynder and Lemon’s series\(^9\) when Seventh Day Adventist males and females were studied and the incidence was 40% less than that expected on the basis of the experience with the entire patient population of the hospitals studied.

Reporting on the original prospective observations of the Hammond-Horn study, Hammond\(^10\) has recently re-emphasized the significant association between cigarette smoking and coronary artery disease. The death rate from coronary artery disease increased rapidly with the amount of cigarette smoking and was nearly 2\(\frac{1}{2}\) times as high among men who smoked two packs or more of cigarettes a day than among men who never smoked, whereas the rate for men who had stopped smoking for a year or longer was lower than for those who continued to smoke cigarettes. The same association, therefore, holds as it did in the case of lung cancer, and any alternative hypothesis must answer identical challenges in accounting for the three main findings of a higher death rate in smokers than non-smokers, an increasing death rate with increasing exposure, and a falling death rate in “discontinued smokers”. The hypothesis that people with a predisposition to coronary artery disease have a desire to smoke cigarettes most assuredly does not explain the third of these findings, nor has another factor or habit become apparent which shares the magnitude of the association that is exhibited by cigarette smoking.

If this association is accepted, isolation and elimination of the noxious agent becomes the next stage in epidemiological study of the relationship. The known acute biological effects of nicotine on the heart and circulatory system long ago led to suspicion that smoking might be related to heart disease. As early as 1938 Pearl\(^11\) showed death rates of all diseases to be higher in smokers than non-smokers and to increase with the amount of smoking, and by 1940 English, Willis and Bker\(^12\) established an association with coronary artery disease death rates. The possibility that nicotine is the responsible agent has stimulated reduction in nicotine content of cigarettes from an original level of 2.5 mg. to levels now less than 1 mg.\(^13\) The continuing smoker should at least take cognizance of this fact on the same basis as the dose-response studies of tar-fraction importance in lung cancer.

This seeming relationship, then, between cigarette smoking and other serious diseases, in association with the higher death rates in smokers, quite properly strengthens the hand of those who feel that the public should be warned about these dangers and that the medical profession as a group should be in the forefront of such progressive public education.

**SUMMARY**

Lung cancer has become one of the most important causes of death. Consideration is given to related factors of epidemiology, etiology and pathogenesis.

In proper epidemiological sequence attention is given to retrospective studies, prospective studies, identification of the responsible agent, and attempts at its elimination or reduction in cigarette smoke. Final emphasis is laid on a relative test of the thesis that the association between cigarette smoking and lung cancer is statistically valid as indicated by the marked reduction in lung cancer incidence and mortality in “discontinued smokers”.

The biological differentiation between “squamous-undifferentiated” carcinoma and adenocarcinoma is
emphasized. Cigarette smoking is related only to the increasing incidence of the squamous type of lung cancer.

The relative hazard of cigarette smoking as compared with pipe or cigar smoking appears dependent primarily on habits of inhalation.

Sequential changes in the bronchial epithelium seem to be associated with exposure to cigarette smoke and become progressively more noticeable with increasing exposure. The potential significance of squamous metaplasia and areas of stasis in permitting prolonged application of a carcinogenic agent is reviewed.

Stress is laid also on the concentration of carcinogens in the butt portion of the cigarette. Methods by which the inhalation of carcinogens may be reduced are outlined.

Difficulties in public education are mentioned but not in any way to minimize the importance of continuing emphasis on the value of such attempts to make the public aware of the adverse effect of cigarette smoking.

Additional respiratory effects of cigarette smoking are summarized with recognition of the relationship to chronic bronchitis and emphysema.

Other factors which might be related to the increasing significance of lung cancer are discussed, noting possible genetic or constitutional attributes of the host and other environmental agents. None of these are thought to demonstrate the magnitude of association found in cigarette smoking, although the importance of atmospheric pollution cannot be overlooked. A reasonable assumption of a cumulative effect of smoking and pollutants is entertained.

The association between cigarette smoking and other diseases, particularly coronary artery disease, is noted. The wide range of diseases affected is not thought to invalidate any conclusions regarding the importance of cigarettes in any one disease. In this relationship one need not assume cigarette smoking to be primarily "causative". Its effect may be on a basis of aggravation and still remain significant.

CONCLUSION

The relationship between lung cancer and cigarette smoking appears inescapable. The facts warrant presentation to the public without the contradictory claims heretofore apparent. The medical profession must no longer fail to accept responsibility in this regard.

REFERENCES