The suggestion has been put forth that chronic bronchitis is a bridge between lung cancer and obstructive lung disease. At present evidence from several sources incriminates cigarette smoking in the production of chronic bronchitis, though not alone, since nonsmokers also have this condition. Nevertheless, reduction of cigarette smoking is of primary importance.

SMOKING AND RESPIRATORY DISEASE

Donald O. Anderson, M.D., F.R.C.P. (C)

There seems little doubt whatever that cigarette smoking, and to a lesser extent other forms of tobacco smoking, are associated with mortality from lung cancer. This association has been amply demonstrated by both case history and cohort studies in a variety of countries, and has been thoroughly summarized at countless symposia and in innumerable review articles. The controversy, instead, is whether this association has the attributes of a cause-effect relationship.

The epidemiologic journey that we have all been forced to travel over the past decade has demonstrated the complexity of this association; we have learned much about the people who get lung cancer and why they smoke, what their parents died of, where they live, and what possible carcinogens they have been exposed to. This journey has not, it seems to me, brought us nearer to our destination—resolving the controversy of the causal effect of smoking upon lung cancer.

The critical step in the evaluation of this hypothesis, the deliberate manipulation of the suspected causal factor to produce predicted changes in the effect, is, alas, lacking. Any natural experiment comparing differences in cancer mortality between smokers and nonsmokers can now be pronounced invalid, since there has already accumulated sufficient evidence to indicate that constitutional factors are associated with smoking and therefore assumptions of random selection are incorrect. Ultimately we must make our own judgment from the analytic evidence at our disposal.

Berkson, commenting on the lack of specificity of the association between smoking and lung cancer, has suggested that the more general association between smoking and all disease is a peculiar one which ought not to be investigated at the organ level. A general effect of smoking, such as accelerated biological aging, does not invalidate a hypothesis that the respiratory system, particularly the lower respiratory tree, is a target organ for the action of a factor which has also other profound biological effects. Indeed, there is no valid objection to the hypothesis that these general biological effects are related to subtle changes in cellular metabolism consequent upon small changes in the function of the lung; at the moment, however, this hypothesis does not lend itself to operational examination.
The semantic difficulties in the study of the association between smoking and lung cancer have not been limited to the word "cause"; the word "carcinogen" has had its share of attention in the controversy. One of the problems has been the high frequency of changes in the tracheo-bronchial epithelium of smokers, whereas only a fraction of the population self-exposed to tobacco smoke develops an overt neoplasm; further, these changes apparently regress when smoking is stopped so that the proportion of ex-smokers which now develops an overt neoplasm is not much greater than that of persons who have never smoked. A "carcinogen," as presently defined by the experimental pathologist, does not behave in this way. Further, despite a wide range of smoking intensity and some variation in the age at which smoking is started, lung cancer appears destined, by some other factor or factors, to appear at the end of the biologically reproductive period; it appears, therefore, to be more a function of chronological age than of duration of exposure to tobacco. I say "appears" since I am by no means satisfied that this observation has not been profoundly affected by biases inherent in case history studies.

As a consequence of these problems we might prefer Kotin's more general hypothesis for the action of cigarette smoke: that "by virtue of its irritant properties and by virtue of the attenuating effect it has on the respiratory epithelial defenses of the host, it provides an excellent local environment for carcinogens, independent of their source, to act."5

I cannot avoid pointing out at this juncture that this hypothesis changes our program of public health action very little. Our research may shift to a search for and removal of the irritants postulated to be in tobacco smoke, but the most effective program remains a general decrease in smoking.

Lung Cancer and Chronic Nonspecific Respiratory Disease

In the light of this more general hypothesis of the action of cigarette smoke, an association between chronic nonspecific respiratory disease and lung cancer would be interesting and meaningful. I use the term "chronic nonspecific respiratory disease" in the same sense as that used by the Ciba Guest Symposium where it refers to asthma, chronic bronchitis, obstructive pulmonary emphysema, and their combinations. It is conceivable that these diseases, and particularly chronic bronchitis, might make the bronchial epithelium a target organ for the action of a carcinogen—found inside or outside cigarette smoke.

Certain epidemiologic similarities between lung cancer and the chronic nonspecific respiratory diseases may be noted from mortality statistics. Both have shown an epidemic increase in Canada, the United States, and England and Wales. Both have a somewhat similar urban-rural differential mortality. Both have a predilection for the male sex and for persons in middle age. In Britain, both increase with successively lower social class for men. There is a significant rank correlation of +0.67 between deaths from respiratory diseases (International List Nos. B31 and B32) and from lung cancer (160-165) in 1955 for the 14 countries Mork selected (to examine for the correlation between lung cancer and cigarette consumption 15 years previous). These observations do suggest an epidemiologic similarity between these afflictions of the respiratory tract. It will also be recalled that Case and Lea found a twofold excess of deaths from cancer of the lung and pleura in World War I veterans pensioned for chronic bronchitis, and that Reid found that London postal employees who suffered from chronic bronchitis had more lung
cancer than predicted from those who did not have bronchitis.

**Smoking and Chronic Nonspecific Respiratory Disease**

The three most widely reported prospective studies of smoking\(^{13-15}\) have demonstrated that the relative risk of death from the chronic nonspecific respiratory diseases is many times higher in cigarette smokers: the largest series which Dorn\(^{15}\) compiled indicated the mortality from bronchitis and emphysema (500-527) to be 3.27 times as great in current regular cigarette smokers than in persons who have never smoked or smoked only occasionally. The data of Doll and Hill\(^{13}\) show a relationship between amount smoked and disease while those of Dorn do not. The prospective studies have also shown a mortality risk for pipe and cigar smokers which is not much greater than for nonsmokers.

It is unfortunate that it is still necessary to consider the chronic nonspecific respiratory diseases as a single nosological unit when we examine mortality rates. We have recently concluded that certain rather striking provincial variations in the death rates for these diseases in Canada are probably best explained by the fact that physicians do not categorize these deaths in any similar fashion.\(^6\) Pulmonary emphysema, which is defined by pathologic criteria,\(^6\) is an end stage, usually, but not exclusively, following a history of chronic bronchitis; somewhere a reversible obstructive condition fits into the picture (it is frequently seen in emphysema)—but it is doubtful that its epidemiology is the same as that of allergic asthma. It will take time to sort out the interrelationships; careful prospective studies must yet be completed before the risks consequent upon chronic bronchitis, its euphemism "smoker's cough," childhood bronchitis, and chestiness, can be appreciated.\(^{16,17}\)

Population surveys of chronic nonspecific respiratory disease prevalence have contributed a great deal to our knowledge of the relationship of these diseases to current cigarette smoking. Through a standard questionnaire and simple pulmonary function tests, chronic respiratory disease can be identified and classified\(^8\) and can be related to other variables under study. In the survey of Berlin, N. H., of 1961, the prevalence of chronic bronchitis was found to increase consistently in either sex with increasing cigarette smoking habits up to a fivefold increase in the prevalence for those smoking more than two packs a day.\(^{18}\) Similar smoking-intensity gradients of disease were noted for the signs and symptoms of more severe obstructive lung disease.\(^{18}\) Higgins has reviewed his experience with a similar methodology\(^19\) and has noted the smoking-intensity gradient only for the mildest symptoms of chronic bronchitis. Other British studies\(^{20,21}\) have failed to show even this smoking-intensity-disease gradient though they have shown that smokers have a higher risk of chronic bronchitis than nonsmokers. This can be attributed to the practice of British investigators to combine all types of tobacco smoked into "cigarette equivalents," thus diluting the effect of cigarette smoke by those other products which are used more by the elderly and which are associated with less disease.\(^{18}\)

A number of geographic comparisons of chronic respiratory disease prevalence, estimated by this type of survey, have been reported\(^{10,22,23}\) and differences in population smoking habits have been noted to parallel differences in disease prevalence. The situation is not so simple. In the Berlin survey\(^{18}\) a significant effect on chronic bronchitis and obstructive lung disease prevalence was produced by the interaction of age and current cigarette smoking intensity. This was observed in men, not in women. It has been diagrammed as a three-dimensional graph in Figure 1 for all chronic
respiratory symptoms, and the data are given for both sexes in Tables 1 and 2. Age-smoking intensity specific rates (hopefully from larger samples) should probably be used in geographic comparisons, though even this may be inadequate because of observed geographic differences in the manner of cigarette smoking.24,25

We have recently compared the respiratory disease prevalence in the city of Berlin, N. H., with that in a small rural town, Chilliwack (population 8,259 in 1961) in the lower Fraser Valley of British Columbia. A current survey of air pollution in Chilliwack is still in progress though there is, as predicted, a fraction of the pollution found in Berlin. The prevalence of chronic bronchitis in men 25-74 years was only 21.5 per cent at Chilliwack compared to about 30 per cent at Berlin. When age and cigarette smoking intensity were simultaneously taken into account, the observed prevalences of chronic bronchitis and obstructive lung disease in Chilliwack were not found to be significantly different from those predicted from the experience at Berlin. Thus, for these two populations surveyed in a similar manner and by the same workers, the urban-rural gradient for the chronic nonspecific respiratory diseases in men can be explained by age and smoking differences.

This overwhelming contribution of age and smoking to the prevalence of chronic nonspecific respiratory disease can interfere in studies of small samples by obliterating a less powerful effect of a variable one hopes to measure.26 Perhaps a smoker so pollutes the air which enters his tracheo-bronchial tree that the biological effects of other sources of pollution are not readily apparent. One approach has been to study the effect of different levels of air pollution on nonsmokers. This has been done for Seventh-Day-Adventists in California,27 and we have examined unsuccessfully for differences between nonsmokers by age, living in different areas of SO2 pollution in Berlin,28 and between Berlin and Chilliwack.

![Figure 1](image-url)
Table 1—Prevalence of Chronic Nonspecific Respiratory Disease by Age and Current Cigarette-Smoking Intensity, in 532 Males, Berlin, N. H., 1961

<table>
<thead>
<tr>
<th>Smoking Intensity (Current Cigarettes/day)</th>
<th>Disease*</th>
<th>Age</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
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<td>45-54</td>
<td>55-64</td>
<td>65-74</td>
<td></td>
</tr>
<tr>
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<td>(28)</td>
<td>(29)</td>
<td>(62)</td>
<td>(63)</td>
<td>(200)</td>
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<td>45</td>
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<td>4</td>
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<td>45-54</td>
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<td>(61)</td>
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<td>55-64</td>
<td>65-74</td>
<td></td>
</tr>
<tr>
<td>All disease</td>
<td>(23)</td>
<td>(22)</td>
<td>(18)</td>
<td>(22)</td>
<td>(18)</td>
<td>(103)</td>
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<td>9</td>
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<td>55-64</td>
<td>65-74</td>
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</tr>
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<td>(7)</td>
<td>(14)</td>
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<td>(12)</td>
<td>(6)</td>
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<td>9</td>
<td>6</td>
<td>29</td>
<td></td>
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<td>3</td>
<td>3</td>
<td>5</td>
<td>1</td>
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</table>

* Defined in reference 16.

Table 2—Prevalence of Chronic Nonspecific Respiratory Disease by Age and Current Cigarette-Smoking Intensity, in 607 Females, Berlin, N. H., 1961

<table>
<thead>
<tr>
<th>Smoking Intensity (Current Cigarettes/day)</th>
<th>Disease*</th>
<th>Age</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
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<td>25-34</td>
<td>35-44</td>
<td>45-54</td>
<td>55-64</td>
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<tr>
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<td>(69)</td>
<td>(139)</td>
<td>(72)</td>
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<td>5</td>
<td>8</td>
<td>9</td>
<td>29</td>
<td>22</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Obstructive disease</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>17</td>
<td>11</td>
<td>39</td>
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<tr>
<td>1–20 (Sample size)</td>
<td></td>
<td>25-34</td>
<td>35-44</td>
<td>45-54</td>
<td>55-64</td>
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<tr>
<td>All disease</td>
<td>(38)</td>
<td>(35)</td>
<td>(40)</td>
<td>(31)</td>
<td>(10)</td>
<td>(154)</td>
<td></td>
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<tr>
<td>Chronic bronchitis</td>
<td>8</td>
<td>7</td>
<td>14</td>
<td>8</td>
<td>3</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Obstructive disease</td>
<td>5</td>
<td>4</td>
<td>12</td>
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<td>27</td>
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<tr>
<td>&gt;20 (Sample size)</td>
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<td>35-44</td>
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</tr>
<tr>
<td>All disease</td>
<td>(11)</td>
<td>(17)</td>
<td>(10)</td>
<td>(7)</td>
<td>(1)</td>
<td>(46)</td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>18</td>
<td></td>
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<tr>
<td>Obstructive disease</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

* Defined in reference 16.

But, perhaps the nonsmoker is the wrong subject after all. Perhaps the heavy smoker, or the person who already has chronic bronchitis, would be the more sensitive indicator of the effect of air pollutants, as was demonstrated in Reid’s study of London postmen.12 Fletcher23 has observed there is very little difference in the prevalence of chronic bronchitis as it was defined at Berlin,28 between men living in the New Hampshire town and those living.
in all areas of Great Britain. Fletcher calls this "simple bronchitis." It is the prevalence of advanced bronchitis characterized by frequent chest illnesses and dyspnea which is more prevalent in Britain and perhaps demonstrates the effect of air pollution.

Does Smoking Cause a "Disease"?

At this point it might be asked whether simple bronchitis, so related to smoking, is really in fact a disease. Can such a condition, which affects 20-40 per cent of the adult American population, be of much pathologic significance? After all, it is common experience that most persons who have chronic bronchitis and who smoke either lose their bronchitis or have a marked reduction in their daily phlegm when they stop smoking.

This chronic productive cough is related to pathophysiologic changes in the tracheo-bronchial tree: tobacco smoke interferes with ciliary action, slows the flow of the mucous blanket, and changes the consistency of the mucus.29 Smoking has been shown to be associated with a hypertrophy of the bronchial mucous glands30 with cellular abnormalities in the tracheo-bronchial epithelium31 which appear to decrease when smoking stops3; some cellular changes, however, appear to be related to age, sex, and residence (urban and rural), as well as to cigarette smoking habits.3

A decrease in vital capacity, increase in residual volume, and evidence of obstruction have been reported by some investigators.21,31,32 In the Berlin, N. H. survey18 there was noted an almost regular decrease in the mean forced expiratory volume in one second (FEV1.0) with increasing intensity of cigarette smoking for each age group. This single test is more discriminatory than other simple tests of ventilatory capacity33 in identifying obstruction to airflow in the tracheo-bronchial tree. The relationship between smoking and the FEV1.0 is more complicated, however. Table 3 is a list of the coefficients and constants for the best fit multiple regression equation relating age, height, and FEV1.0 in the full sample of 562 Berlin, N. H., men. Most male smokers under 45 have better values for this test than nonsmokers of comparable age and height; indeed, this effect was so striking we could not compare our nonsmoker nomograms with those published as "normal" by others. Seltzer's study34 of the 1942 Harvard University entrants may indicate the reason: persons who later become smokers he found to be greater in chest circumference relative to height. Nevertheless, despite this physical headstart which might even be related to the tyro smoker's tolerance of tobacco, all male cigarette smokers in the Berlin area except those smoking less than half-a-pack a day show a greater decline with age than those who have never smoked cigarettes. The intersection of these regression lines with the line for those who have never smoked cigarettes standardized to 170 cm tall is shown in Table 3; after age 41 the person who has never smoked or who is currently smoking ten or less cigarettes a day consistently has better lung function.

Though many acute studies of cigarette inhalation have failed to show any effect on mechanical factors of respiration in healthy subjects, more recently, by a different technic, a 25-30 per cent decrease in airway conductance has been reported immediately after inhalation of cigarette smoke35; this bronchoconstriction occurs similarly in both smokers and nonsmokers, is rapidly reversible and recurs after a second cigarette. The inhalation of pharmacologically inert submicronic particles can produce this reaction which is likely mediated through the vagus nerve.

The evidence points to the fact that smoking is the most important, though not the only, factor in the production of
simple bronchitis, and that with time bronchial obstruction is produced; initially this obstruction is probably reversible but with further exposure more serious irreversible obstructive disease of the lung is produced. Bates16 regards impaired diffusing capacity of the lung (DLCO) as evidence that chronic bronchitis has progressed to pulmonary emphysema. It is of interest that a significant decrease in DLCO has been found in smokers and has been reported to occur somewhere after five to ten years of smoking a pack or more of cigarettes a day.36

From the epidemiologic study at Berlin, N. H., a similar latent period or threshold was noted18: in both men and women the relative risk of the prevalence of chronic bronchitis and obstructive lung disease doubled over that of those who had never smoked cigarettes somewhere between 3,000 and 6,000 packs of lifetime smoking; i.e., after at least eight years of smoking at the rate of a pack a day.

General

We have reviewed, all too briefly, an exceedingly complex subject, one in which new knowledge is appearing daily. It has been suggested that chronic bronchitis is a bridge between lung cancer and irreversible obstructive lung disease. At the moment, epidemiologic, pathologic, and physiologic evidence incriminates cigarette smoking in the production of chronic bronchitis, though not solely so, for nonsmokers also have this disease.

What should be the public health action to deal with bronchitis? Certainly, control of air pollution will contribute, somewhat. But bronchitis is clearly related to another form of air pollution which is self-induced—tobacco smoking. It seems inefficient to plan an effective control program which does not attack the practice of cigarette smoking first.
REFERENCES


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This paper was presented before the Epidemiology Section of the American Public Health Association at the Ninety-First Annual Meeting in Kansas City, Mo., November 11, 1963.

This study was supported in part by Dominion of Canada National Health Research Grant (Project No. 609-7-73) and a research grant from the United States Public Health Service (OH-67).