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Critical Reviews

DOES CHRONIC IRRITATION CAUSE PRIMARY CARCINOMA OF THE HUMAN LUNG?

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Primary cancer of the lung, in common with other forms of malignant growth, is almost universally believed to originate through some form of chronic irritation, which usually sets up a chronic inflammatory process in the bronchial mucosa. The literature contains many examples of this view. Thus Davidson [1] stated: "Numerous theories have been advanced, mostly relating to the factor of irritation in some form or another of the respiratory tract, to account for this phenomenon." Simons,[2] who listed fourteen causes, found chronic irritation of the bronchial mucosa a factor common to all of them and concluded that this common factor is the cause of pulmonary cancer. Fried [3] said: ". . . it is beyond doubt that irritation is as necessary a predisposing factor in the causation of cancer of the lungs as it is in cancer of other organs." In the minds of the commentators it seems to make but little difference what the irritant is, so long as it is an irritant, and there are various types, such as mechanical, chemical, thermal, bacterial, electrical and radioactive. Often more than one type is at work on a given region, as when an area of the tongue's surface is persistently scratched by a sharp stump of a tooth (mechanical) with erosion of the epithelium and exposure of the unprotected tissues to irritants of bacterial and chemical types. The sine qua non seems to be that the irritant shall act constantly or at short intervals over a *long period*. There is no agreement as to the length of time that is required in any given case to produce a cancer; it is conceded that this factor is a variable one, and operates in association with other variables, such as age, anatomic site and predisposition. The irritant, too, must

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1. Davidson, M.: Cancer of the Lung and Other Intrathoracic Tumors, Bristol, England, John Wright & Sons., Ltd., 1930.

2. Simons, E. J.: Primary Carcinoma of the Lung, Chicago, The Year Book Publishers, Inc., 1937.

3. Fried, B. M.: Primary Carcinoma of the Lung, Baltimore, Williams & Wilkins Company, 1932.

act sufficiently strongly to produce an effect in the tissue but not so strongly as to cause total necrosis of the tissue.

It seems certain also that in most if not all cases inflammation supervenes in the region undergoing exposure to the irritant. The inflammation is a reaction on the part of the tissues to the injury occasioned by the irritant. It may, theoretically at least, be regarded as protective in nature, though the means sometimes defeats the end, as in silicosis. Since chronic inflammation is a well nigh inevitable and universal concomitant of chronic irritation, the one term has often been used as synonymous with the other, and thus it is that chronic inflammation is regarded as the etiologic agent in primary cancer of the lung, without any distinction being made between the fundamental irritating agent and the tissue responses following its chronic action. So widespread is this usage with regard to chronic inflammation, indeed, that we find it convenient, in the following pages, to discuss the alleged causes of primary cancer of the lung under headings of the pathologic conditions, generally inflammatory in nature, rather than of the specific irritants. Commentators have found it difficult, too, to distinguish between chronic inflammation per se and the chronic reparative process, and it would seem that the two phenomena are so involved, one with the other, as to be practically inseparable. Thus, if we were accurate, we should ascribe the growth of the cancer to the hyperactive repair process, with its urge to increased cell multiplication, reserving to chronic inflammation or to some other factor the carcinogenic influence which first sets a cell or cells on the cancerous path.

It is our purpose in this review to bring forward data indicating *that the thesis that primary carcinoma of the lung is due to chronic inflammatory changes in the lung is unproved*. We do not feel justified as yet in denying outright that chronic inflammation causes pulmonary cancer, but we affirm that on the whole the evidence now available does not warrant such an assumption. Even the carefully selected, so-called positive evidence that is commonly regarded as supporting the thesis is by no means unequivocal.

That chronic inflammation should have been implicated as the cause of cancer is not surprising, for the two are often present in the same region. We would point out, however, that because primary cancer of the lung is not infrequently found associated with chronic inflammatory changes is no reason for assuming that it necessarily is due to these changes. Indeed this association no more justifies the conclusion that the cancer is so caused than does the circumstance of a man being found near the scene of a crime establish beyond doubt that it was he who committed the crime. His presence at the scene may have been merely fortuitous. It seems quite possible that chronic inflammation often stands in relation to primary cancer of the lung as does the innocent man at the

site of the crime. Indeed, in many cases the inflammatory changes are neither the cause nor a chance associate of the cancer but are its result.

Moreover, even if at some future time adequate proof should be forthcoming to show that in some cases chronic inflammation or irritation is the extrinsic cause of pulmonary cancer, such proof can be used only in mass data, not in individual cases. There are persons who present no evidence whatever of chronic inflammatory disease of the lungs who nevertheless show development of cancer of the lung, and, on the other hand, there are persons who, despite having suffered from inflammatory diseases of the lungs for years, never have cancer of the lung. It is impossible to say of any one case that had the chronic inflammatory change not existed cancer of the lung would not have developed.

ENVIRONMENT AND HEREDITY IN THE ETIOLOGY OF PRIMARY CANCER OF THE LUNG

As with all other cancers, the problem of the origin of primary cancer of the lung naturally divides itself into two aspects concerned with (1) supposed productive factors acting from outside the body and (2) constitutional factors inherent in the body and varying with the patient and particularly with the "strain" or line of descent. These agencies are characterized as environmental and hereditary, respectively. The environmental factors may be subdivided into two categories: (1) those that would be encountered in the course of ordinary living, which are the various chronic irritants commonly used to explain human cancer, and (2) those which have been discovered by inducing cancers in animals through the experimental use of specific chemical agents, called carcinogens. As man is not used in the experimental production of cancer, all malignant growths arising in him must come under the heading of (1) tumors induced by the chronic irritations of ordinary life or (2) tumors arising on account of constitution. These may be considered as primary poles, or extremes, useful in our mental processes in the study of the causes of cancer. Actually, the constitutional factor enters into every production of tumor, and the only point which needs to be determined with reference to it is the extent to which it is participating in any given case. So, if the environmental factor is admitted, all tumors are of dual origin.

We shall now review briefly the sources of so-called chronic irritation to determine what proof has been brought forward to sustain the thesis that chronic irritation causes pulmonary cancer in man. A large number of citations from the literature might be made in support of the idea that chronic irritation, especially in the form of chronic inflammatory change, is responsible for the genesis of primary cancer of the lung.

These would be, in practically all cases, merely opinions without any valid basis of proof. They might be encountered with an equally large number of statements questioning the role of chronic irritation in the causation of primary cancer of the lung. These, again, would be opinions, for the most part, with no proof to sustain them. They would show two things, however: first, that the theory of chronic irritation has not been accepted without question and second, that the burden of proof should rest on those who assert that primary cancer of the lung in man is caused by chronic irritation or inflammation.

ALLEGED ENVIRONMENTAL CAUSES OF PRIMARY CANCER OF THE HUMAN LUNG

Simons[2] listed a number of supposed general causes of primary pulmonary carcinoma in man, and in them he finds a common factor, namely, chronic irritation. These alleged causes should be divided into two sections: (1) those capable of being produced by pulmonary cancer (these are often found associated with such cancer because they are sometimes the results of the presence of the cancer either alone or in combination with other influences); (2) those which are not capable of being produced by cancer of the lung but which might be found associated with it in the same patient in a varying percentage of cases. With regard to group 1, it might well be that in some instances these conditions have been present before the cancer ever started, although they are not necessarily the cause of the cancer, while in others these conditions have not been present until after the cancer started and are a direct result of the growth of the tumor. We shall now discuss the conditions which belong to group 1. They are chronic bronchitis, pulmonary abscess, asthma, bronchiectasis, pleurisy, emphysema and conditions simulating pneumonia and influenza. The conditions listed in group 2 by Simons[2] are trauma, tuberculosis, pneumonoconiosis, chalicosis, syphilis, roentgen irradiations, inhalation of dust (especially from tarred roads), smoke (especially if bearing chemical irritants, as in certain of the industries), motor exhaust fumes and war gas, various industrial and occupational hazards involving the breathing of hot air (especially if bearing chemical fumes), tobacco smoke or the air of certain mines, such as those of Schneeberg, Bohemia, which contain not only irritant dusts but radioactive substances as well. It will be found that as industry expands and new chemicals are encountered, this second list of conditions which are supposed either rightly or wrongly to cause cancer of the lung will increase.

Let us review first the course of development of a cancer of the lung, so that we may see why the conditions in group 1 are so often found associated with this malady.

COURSE OF DEVELOPMENT OF TYPICAL CANCER OF THE LUNG

Although no one has followed the course of a cancer of the lung from its onset to its full expression, the following outline is regarded as probably accurate: The epithelium in some local region of the bronchus undergoes a change which makes it "malignant" to the rest of the body. At this point we are not discussing what the nature of the change is, or whether this change is occasioned by forces inherent in the cells or is brought about by extrinsic influences. The cells whose ability to differentiate into normal cells and to organize into normal tissue has been wholly or partly lost still retain their ability to grow and do grow. The growth at first is probably slow. This is the beginning of the tumor. In time the tumor causes a narrowing of the bronchus, so that an obstruction to airflow ensues, together with a handicap to the normal bronchial eliminative mechanism. This impairment of function is followed by degenerative changes in the part of the lung served by the involved bronchus. The irritation produces a cough, often nonproductive at first, of chronic character, which simulates that of chronic bronchitis. Inflammatory changes in the mucous membrane follow the damming back of the excretions normally wafted away by the cilia or removed by the peristaltoid action of the bronchus or by coughing. The cough grows worse, and blood-streaked sputum is produced. When the obstruction to the bronchus is complete, either through blocking of the lumen by the growth within or by pressure on the bronchus by the encircling growth without, there is atelectasis in the lung beyond the point of obstruction. This is followed by bronchiectasis of the bronchi in the collapse area, which dilate to make up for lost volume of lung. Another effect of the diminution in volume of lung is compensatory emphysema in the alveoli of the surrounding lung tissue. These become more dilated with coughing. An asthmatic wheeze may develop in the narrowed bronchus before it is completely obstructed.

If the center of the tumor becomes infected and undergoes necrosis, the patient may show an abscess of the lung with drainage of the pus through the bronchus. If the tumor grows extensively toward the periphery of the lung before it breaks down, the pleura becomes inflamed, and pleural effusion results. The pus may rupture into the pleural cavity, and the patient may be operated on for empyema without the cancer of the lung being recognized. The onset of the symptoms may be acute and simulate influenza or pneumonia; or the onset may be gradual, and tuberculosis may be diagnosed. In any of these steps an erroneous diagnosis may be made, and the patient may later, when the cancer is discovered, assume that the "chronic bronchitis," "influenza," "asthma" or "tuberculosis" which he was supposed to have was the *cause* of the cancer. The physician sometimes accepts at face value statements to

the effect that the patient had chronic bronchitis for some time before the cancer was recognized and that the one was therefore the cause of the other.

The course of bronchogenic cancer, as is probably true for all other cancers, can be divided into three periods: First, there is a "silent" period, which lasts from the moment of the initial change of normal cells into cancer cells up to the time when symptoms of such severity begin that the patient associates them with the onset of his illness. This stage is apparently the longest and is completely silent as far as the localized activities are concerned (though symptoms may be produced from a metastasis in some other region) but may give rise to vague general symptoms. The second, or symptomatic, period is characterized by the onset of symptoms, which progress up to the time of the diagnosis of cancer of the lung, or until death if the diagnosis is not made. This period may be relatively brief, only a few months, or at the most it may be a few years. The third period is the "diagnosed" stage and is usually the briefest; it is nonexistent if the diagnosis is not made. In most cases it lasts from the time of diagnosis of cancer of the lung until death, for relatively few patients have been operated on and cured, even for a brief time.

It is evident, then, that because of the initial silent period there is trouble in ascertaining whether any particular chronic inflammatory disease preceded the onset of the cancer of the lung. Thus bronchitis, coming before the "diagnosed" period, is thought to antedate the cancer, although the cancer existed in the silent period before the onset of the bronchitis. The symptomatic period, before cancer of the lung is recognized, during which the patient may have various pulmonary symptoms, helps to confuse cause and effect of cancer of the lung and to make patient and physician alike interpret the symptoms produced by the cancer as symptoms of conditions giving rise to the growth.

SPECIFIC SO-CALLED CAUSATIVE FACTORS OF CANCER OF THE LUNG: GROUP 1

Chronic Bronchitis.—Chronic bronchitis has been looked on by some writers as of importance in the etiology of cancer of the lung because (1) it produces chronic inflammation of the bronchial mucosa and (2) it is found with some frequency in the histories of patients with cancer of the lung. What evidence is there to support or to deny the assertion that chronic bronchitis plays a causative role in pulmonary cancer? One of the first arguments that will occur to any one is that bronchitis may be generalized in distribution, while cancer of the lung is localized. The inflammatory changes of bronchitis are widespread and peripheral as well as central, while cancer of the lung is localized and is usually hilar.

If chronic inflammatory changes induce the cancer, why does not the cancer originate diffusely over the lung?

Chronic bronchitis has no special predilection for the male sex, but cancer of the lung occurs about four times as often in males as in females. It would seem, if chronic bronchitis is a major cause of cancer of the lung, that men should be much greater sufferers from bronchitis than are women, yet no such preponderance has been mentioned in the texts on diseases of the lungs, and mortality statistics do not show more deaths from bronchitis in males than in females.

Although it might be assumed that the regeneration of the bronchial epithelium in chronic bronchitis would lead to cancer of the lung, we must ask if there is proof that it does so. First, is bronchitis followed more often by cancer of the lung than not? Second, how many patients with cancer of the lung give a history of chronic bronchitis that is of such long duration that it can legitimately be looked on as having antedated even the silent period of the cancer's growth? There are no adequate answers to either of these questions because we do not know how many persons in the population have chronic bronchitis and we have little idea of how long the silent period can be. Since most takers of clinical histories content themselves with stating that the patient had complained of chronic bronchitis, failing to give the time during which the bronchitis existed, we cannot place much reliance on reports in which it is merely stated that a certain percentage of patients with cancer of the lung have had bronchitis. First, we should have to exclude all those in whom bronchitis probably followed instead of antedated the silent period of the pulmonary cancer.

Since we know that cancer in general is slow growing, and that in men who have worked in the Schneeberg mines cancer of the lung may develop from ten to twenty-seven years after they have been pensioned off from work in the mines, we should probably have to allow a minimum of at least ten years before the cancer was diagnosed as the period during which it was probably present in the silent stage. Therefore, all patients with cancer of the lung in whom chronic bronchitis started within the last ten years before the diagnosis of cancer of the lung was made should be excluded as most probably being patients in whom the cough was either the result of the tumor or coexistent with it though not actually caused by it. Those who had a history of cough for more than ten years might possibly be looked on as patients in whom the cough antedated the cancer, although this would not inevitably be so. Second, we should then compare the latter group of patients with the general population in regard to the incidence of chronic bronchitis. If 10 per cent of the population past 40 have a history of chronic bronchitis, we need not be surprised if 10 per cent of patients with cancer of the lung

have a history of chronic bronchitis without there being any cause and effect relationship between the two. If 60 per cent of the general population have had chronic bronchitis, 60 per cent of patients with cancer of the lung may be expected to have had chronic bronchitis antedating the earliest moment of their cancer's growth without its being in any way responsible for the tumor. Unfortunately, we do not have reliable data on the incidence of chronic bronchitis in the middle-aged population, but Maxwell and Nicholson [4] remarked, "The commonest antecedent condition was chronic bronchitis, which occurred in the past history 21 times (100 cases), although when it is remembered that this condition is exceedingly common, the fact is deprived of any great significance." Most of the writers whose observations are cited to show that chronic bronchitis is a causative agent in pulmonary cancer have forgotten two facts: (1) that cancer of the lung causes chronic bronchitis in some of its victims and so explains a certain percentage of the cases in which the two conditions are found, and (2) that unless chronic bronchitis antedating the cancer is found more often in patients with cancer of the lung than in the general population of the same age and sex as these patients, its frequency in the patients with cancer of the lung, however great, is not significant. Moreover, chronic bronchitis, even including that *caused* by the cancer, does not occur in more than about 50 per cent of the patients if one strikes an average from the numerous series of cases reported in the literature.

Thus we can say that chronic bronchitis is by no means universally found in the histories of patients with cancer of the lung, that when it is found it is because the presence of the *tumor has caused the bronchitis* in a large number of the cases, that there is no way of showing that chronic bronchitis which might conceivably have antedated the tumor of the lung is more commonly found in patients with cancer of the lung in the general population and therefore that *the role of chronic bronchitis as a causative agent in the production of pulmonary carcinoma has not been demonstrated.*

Bronchiectasis.—Like chronic bronchitis, bronchiectasis is frequently a result of the presence of primary cancer of the lung, following on atelectasis caused by occlusion of a bronchus by the tumor. Hence this condition might be found either clinically or at autopsy in a large percentage of the cases of primary cancer of the lung, but it is caused by, and is not the cause of, the cancer in the majority of cases (Zacherl [5]). Because a benign tumor of the lung lasts over so much longer a period than does pulmonary cancer, a benign tumor can almost always grow large enough to occlude a bronchus before killing the patient. There-

4. Maxwell, J., and Nicholson, W. A.: Quart. J. Med. **24**:29, 1935.
5. Zacherl, S.: Wien. klin. Wchnschr. **44**:967, 1931.

fore, bronchiectasis is *always* an accompaniment of a *benign tumor of the lung* of any duration, according to Wessler and Robin.[6]

It may be, of course, that a patient who has had bronchiectasis due to some other cause may subsequently have cancer of the lung. In such a case the bronchiectasis preceded but did not necessarily cause the cancer. Many patients have bronchiectasis who never have cancer of the lung; indeed, Graham, Singer and Ballon[7] stated that in patients in whom the primary lesion is bronchiectasis "it is striking that there are but few examples of carcinoma which have developed in a bronchiectatic dilatation."

Until the proponents of the idea that the chronic inflammation caused by bronchiectasis induces cancer of the lung can show that *bronchiectasis which preceded the onset of the cancer* is followed by cancer in the inflammatory zone of the wall of the bronchiectatic cavity in a percentage of cases which is significantly higher than the percentage of cases of cancer of the lung in the population of the same age and sex distribution which is without bronchiectatic cavities, we may conclude that *no relation has been demonstrated between the chronic inflammatory changes occurring in bronchiectasis and pulmonary cancer.*

Asthma.—Asthma, although not primarily inflammatory in nature, may induce chronic thickening of the mucosa as well as of the muscle coats. It has been advanced by some authors as one of the causative agents in cancer of the lung. As in the case of the two conditions just discussed, asthmatic symptoms may result from the presence of a pulmonary cancer, and so a history of asthma preceding the diagnosis of the cancer cannot be accepted as evidence that asthma caused the cancer. On the other hand, true asthma of long duration may be found in persons in whom cancer of the lung later develops, and, again, this need not imply a causal relation between the two conditions unless cancer of the lung can be found in persons with chronic asthma in far greater proportion than in the general population. Again, we have no idea of the true incidence of asthma which antedates cancer of the lung in patients with this form of cancer, since publications based on the clinical histories give for the most part merely a statement that asthma occurred in a certain percentage of cases of cancer of the lung without giving any idea of the length of time during which the asthma had existed before the cancer was diagnosed.

From cases reported in the literature it seems that on the average about 7 per cent of patients with cancer of the lung had a history of asthma. Therefore, even if asthma is looked on as contributing to the

6. Wessler, H., and Robin, C. B.: Am. J. M. Sc. **183**:164, 1932.

7. Graham, E. A.; Singer, J. J., and Ballon, H. C.: Surgical Diseases of the Chest, Philadelphia, Lea & Febiger, 1935, p. 815.

predisposition to pulmonary cancer, it is by no means a universal cause of such cancer, and one has no evidence that it is a cause at all until one can prove that true asthma antedating beyond question the onset of a pulmonary tumor has occurred far more often in patients with cancer of the lung than it has in patients without cancer of the lung. Such proof at present is not forthcoming.

Emphysema.—Pulmonic alveolar emphysema of the degenerative type, with a barrel-shaped chest, overly large alveolar spaces and other signs, is not primarily an inflammatory change associated with regeneration of the bronchial epithelium and cannot reasonably be looked on as productive of cancer of the lung. Emphysema of the compensatory type may be an accompaniment of cancer of the lung in the later stages of the latter, after atelectasis has ensued, and is then a result not a cause of the cancer. The incidence of this condition in the general population is not known, nor is its incidence as a condition truly antedating cancer of the lung known; therefore one can make no reliable deductions as to the role which alveolar emphysema plays in causing cancer of the lung. Such a role has not been demonstrated.

Pulmonary Abscess.—This may be associated with cancer of the lung as a result of the breakdown of the center of the growth, so it is easily understood why such a history should be recorded frequently for patients with cancer of the lung. Funk[8] stated that a pulmonary abscess of obscure cause in a man past 30 should make one suspect that a malignant growth is present.

Pleural Effusion.—An involvement of the pleura in the form of dry pleurisy, a pleural effusion or empyema may be found in patients with cancer of the lung, and not infrequently it is the first symptom of which a patient complains. One of the methods of diagnosis of cancer of the lung is the centrifuging of fluid aspirated from a pleural effusion with a view to finding cancer cells in the sediment. Baker-Bates and Ellis[9] stated that a patient with pulmonary cancer may be treated surgically for empyema for some time without the underlying cause of the empyema being recognized.

Summary.—Summing up the evidence in this group of cases, we find the following conclusions to be justifiable: Because chronic bronchitis, bronchiectasis, asthma, emphysema, abscess of the lung and pleural effusion may be found as a result of the presence of the tumor in the bronchus, it is inevitable that a certain degree of association between these conditions and cancer of the lung will be found in any series of cases of pulmonary cancer. The crucial point to be proved to sustain the theory that these chronic inflammatory conditions actually

8. Funk, E. H.: J. A. M. A. **95**:1879, 1930.
9. Baker-Bates, E. T., and Ellis, G. R.: Lancet **1**:676, 1935.

predispose to cancer of the lung is that their presence actually antedating the probable time of onset of the tumor is found in significantly higher percentages of patients with cancer of the lung than of those without cancer of the lung when the two groups are kept comparable as to age, sex, and industrial occupation where there is the slightest suspicion that such occupation might be a cause of pulmonary cancer.

We have shown that such evidence has not been advanced for any one of the aforementioned conditions because there has been little attempt to separate the patients with cancer of the lung into two groups, those in whom the pulmonary conditions were a result of the presence of the tumor or at least were initiated after the tumor had started to grow, and those in whom the conditions might legitimately be interpreted as having antedated the cancer. There also has been little attempt on the part of those who affirm that these conditions predispose to cancer of the lung to ascertain the incidence of these conditions in the general population of the same age and sex as the group with cancer of the lung. The opinions advanced by the supporters of the idea that these chronic pulmonary conditions cause cancer of the lung have largely been based on the finding of these conditions in an appreciable number of patients with cancer of the lung, without regard to their incidence in the general population. We have shown that no single one of these conditions has been *proved* to be the cause of cancer of the lung. The addition of a number of uncertainties may make a larger number, but it does not add to the accuracy of the result. If none of these has been shown to cause cancer of the lung, the sum total of them has not been shown to cause cancer of the lung, nor has the common factor resident in them, chronic irritation, been shown to be conducive to the formation of tumors of the lung.

GROUP II

We now turn to the second group of so-called chronic irritations listed by Simons [2] which are looked on as causing cancer of the lung but which are not symptoms of the disease itself, although in some instances they may simulate some of these conditions.

Influenza.—In a search for previous infections of the lung which might explain the origin of primary pulmonary cancer and especially its apparently great increase since 1920, workers have suggested that influenza might be a major factor. Askanazy,[10] Winternitz, Wason and McNamara [11] and others found metaplasia in the bronchial epithelium following influenza which in some cases was almost indistinguishable from malignant growth. There is no proof that the epithelial metaplasia

10. Askanazy, M.: Centralbl. f. allg. Path. u. path. Anat. **30**:443, 1919.

11. Winternitz, M. C.; Wason, J. M., and McNamara, F. P.: The Pathology of Influenza, New Haven, Conn., Yale University Press, 1920.

following influenza went on to cancer formation, since carcinoma of the lung has developed in only a very small part of the population who had influenza in 1918 and recovered. In patients who had influenza and who have since died of some other disease there has been no higher incidence of cancerous change in the lungs than in patients who have died without having had influenza. Thus, if 50 per cent of the population now at the ages of 40 to 50 had influenza in the period from 1918 to 1920, one would expect to find that 50 per cent of the patients with cancer of the lung who are now between the ages of 40 and 50 would give a history of having had influenza. Before one may attribute to influenza a part in the causation of cancer of the lung it will have to be shown that influenza has occurred in a far greater number of persons with cancer of the lung than in persons not having cancer of the lung, and even then there would be no conclusive proof that a short attack of influenza, lasting but a few weeks, could produce such lasting changes as to initiate a pulmonary cancer. Even with specific carcinogenic agents, whose effect has been definitely demonstrated, a single application or repeated applications for a short time do not usually result in cancer; to be effective, they must be applied frequently and over a long period or must be introduced into the body in such a way that their effect is continuous.

Other arguments against the role of influenza in causing cancer of the lung are as follows: Influenza is generalized; cancer of the lung is localized. Influenza affects both sexes equally; cancer of the lung predominates in the male sex. The increase in cancer of the lung began to be noted in some countries before the 1918 epidemic of influenza.

Finally, it must be remembered that cancer of the lung may begin its symptomatic period as an attack simulating influenza from which the patient does not completely recover. There is fever, lassitude, cough and then a long-dragged-out partial recovery. The patient says that he had an attack of influenza, but what actually happened was that his pulmonary cancer began to show itself with respiratory symptoms that simulated an influenzal attack. Therefore, before deciding that a history of influenza in a patient with cancer of the lung is indicative that influenza is a causative agent, one must be sure, as with the other diseases discussed, that the disease was true influenza and that it antedated or probably antedated the onset of the cancer; i. e., there should have been a period of at least ten years between the influenza and the diagnosis of cancer. Even that might be too short a time, but anything under that is almost certain to be too brief an interval.

An average derived from numerous series of cases of cancer of the lung reported in the literature shows that in 12.4 per cent the patient gave a history of previous attacks of influenza, some of which may have

been results of the presence of the cancer rather than the cause. Kerley [12] found that although the influenza epidemic had been particularly severe in Iceland, there had been no great increase in the incidence of pulmonary tumor there. Boyd,[13] Hill [14] and Maxwell and Nicholson,[4] among others, have felt that influenza probably does not play any role in cancer of the lung. Until it can be shown that true influenza antedating the diagnosis of cancer of the lung by ten years or more occurs in the history of patients with pulmonary cancer more often than in the history of patients without pulmonary cancer one cannot accept influenza as having been proved to be an agent in producing primary pulmonary carcinoma.

Tuberculosis.—If chronic inflammatory changes are looked on as a possible or even a probable source of cancer of the lung, it is natural that tuberculosis should have been regarded as an etiologic agent because of its chronicity. Ewing [15] felt that tuberculosis was associated with cancer of the lung unduly frequently, but practically all other workers have felt that there was a very infrequent association between the two conditions. Unless tuberculosis and cancer of the lung are mutually exclusive, one should find about the same proportion of pulmonary cancers in persons dying of tuberculosis (provided, of course, that the two groups compared are kept constant in regard to age and sex) as one finds in a population not dying of tuberculosis. The necessity of the proviso is at once apparent, since the highest absolute number of deaths from tuberculosis is usually among the young, and among females. One finds, for example, in Canadian data for 1936 that 1 of every 8 men who died between the ages of 40 and 44 died of pulmonary tuberculosis. Let us assume that all of these had tuberculosis and that none had a cancer of the lung erroneously diagnosed. Also 1 of every 100 men who died at the same age died of recognized cancer of the lung. One would expect, without any significance being attached to the finding, that 1 of every 8 men dying of pulmonary cancer between the ages of 40 and 44 would also have active tuberculosis, and that 1 of every 100 men dying between the ages of 40 and 44 with tuberculosis would also have cancer of the lung.

Chiari [16] stated that from 3 to 12 per cent of patients with cancer of the lung have active tuberculosis. These figures deal with men of all ages dying of tumor of the lung. Again illustrating from Canadian data and taking only men dying after the age of 40, since pulmonary tumor

12. Kerley, P. J.: Brit. J. Radiol. **30**:333, 1925.
13. Boyd, W.: Canad. M. A. J. **23**:210, 1930.
14. Hill, R. M.: Edinburgh M. J. **41**:320, 1934.
15. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.
16. Chiari, H.: Klin. Wchnschr. **17**:183, 1938.

is relatively uncommon before that age, we find that approximately 3.3 per cent of men dying in 1936 in Canada died of what was diagnosed as pulmonary tuberculosis. This probably represents the minimal estimate of men dying with active tuberculosis in Canada in that year. On that basis we should expect approximately 3.3 per cent of males dying of cancer of the lung after 40 to show, in addition to the cancer, active tuberculosis, a figure agreeing with Chiari's[16] data. In countries in which there is far more tuberculosis than in Canada the proportion of patients dying of cancer of the lung who have active tuberculosis, in addition, will be far higher than 3.3 per cent; in countries in which the tuberculosis rate is lower, the proportion will be under 3.3 per cent.

It is found on examining the records of those persons with pulmonary cancer who showed active tuberculosis of the lungs at autopsy that the cancer did not grow in the wall of the tuberculous cavity, where the inflammatory changes were taking place, in the majority of instances. The tuberculosis was more often found in the lung opposite to the one in which the cancer developed than in the same lung, if one can judge from the reports in which the sites of the two diseases were given in the autopsy protocol. Or if the disease was present in the same lung, it was not in the same lobe. Even if the two processes are found in the same part of the lung, which is apparently rarely the case, this still might be due to chance association. Most authors, including Boyd,[13] Maxwell and Nicholson,[4] Chiari,[16] Funk,[8] Hill,[14] Husted and Bellmann[17] and others, have expressed the opinion that there cannot be demonstrated any causative influence on the part of tuberculosis in producing cancer of the lung. Fried[18] said: "It is of interest that the occurrence of tuberculosis and of cancer in the same person or in the same organ is rarely seen at necropsy." This observation taken together with the frequency of tuberculosis in the general population leads one to conclude that tuberculosis does not predispose to cancer of the lung.

Pneumonia.—The onset of cancer of the lung may simulate pneumonia, so that the patient may give a history of pneumonia, which he thinks was the cause of the pulmonary tumor. On the other hand, the patient may have had true pneumonia, either antedating the silent period or antedating the symptomatic period of the cancer, without there being any association between the two. Since pneumonia is by no means an uncommon disease, one would expect to find a great many of the population who have had pneumonia and recovered; therefore one would expect to find an equal percentage of patients with cancer of the lung who have had pneumonia without there being any significance in the

17. Husted, E., and Bellmann, G.: Acta path. et microbiol. Scandinav. **14**:141, 1937.

18. Fried,[3] p. 17.

fact. Thus in Canada, 5 per cent of the men dying after the age of 40 in 1936 died of pneumonia. For every man that died there were probably 3 men who recovered, since the mortality rate in pneumonia is or was at that time about 25 per cent. Therefore we can assume that another 15 per cent of men dying at that age had had the disease at some earlier date but had recovered and died of something else. Therefore we should not be surprised to find that about 15 per cent of patients with pulmonary cancer give a history of having had true pneumonia. The pneumonia may have occurred in the same lobe in which the cancer was to develop or had already developed, or it may have occurred in a different lobe or on the opposite side, as was the case with the patient reported by Graham and Singer.[19]

As to the incidence of the history of pneumonia in cases of cancer of the lung, we find the following data: Parish[20] found this history in 1 of 32 cases; Matz,[21] in 15.2 per cent of 138 cases; Hill,[14] in 10 of 107 cases; Maxwell and Nicholson,[4] in 7 of 100 cases. *These are the figures we should expect if pneumonia has no relation whatever to the production of cancer of the lung.*

War Gassing.—It is not to be wondered at that war gassing has been suggested as a possible cause of pulmonary cancer in some cases. There would seem to be only two possible ways in which war gas might cause cancer of the lung: (1) by a direct carcinogenic effect, in which case it would probably have to be applied repeatedly in small doses over a long period, since a few exposures would probably not induce cancer; (2) by the production of a chronic inflammatory condition in the lung that would be carcinogenic. The first assumption carries little weight, because it has not been shown that war gases have a specific carcinogenic effect and because there is no history of numerous repeated applications of them; the second reason is also without much value, since we have found that none of the chronic inflammatory or degenerative conditions which war gases caused, such as chronic bronchitis, emphysema, asthma, activated pulmonary tuberculosis and pulmonary fibrosis, can reasonably be linked with the development of cancer of the lung.

From data supplied by Matz[21] and by Stein and Joslin[22] on United States Veterans of the World War we see that, of 164 men with cancer of the lung, 8, or 4.8 per cent, gave a history of having been gassed in the war. Maxwell and Nicholson[4] found 4 men from among about 75 to 80 in the age range of World War veterans who had histories of having been gassed in the war and who also had pulmonary cancer.

19. Graham, E. A., and Singer, J. J.: J. A. M. A. **101**:1371, 1933.
20. Parish, T. N.: Practitioner **125**:324, 1930.
21. Matz, P. B.: J. A. M. A. **111**:2086, 1938.
22. Stein, J. J., and Joslin, H. L.: Surg., Gynec. & Obst. **66**:902, 1938.

They held that war gassing has no role in causing cancer of the lung. In order to evaluate adequately the possible role of war gassing in the production of cancer of the lung we need to know the following facts: What is the number of World War veterans living at the present time? What percentage of these were gassed in the war? In what number of World War veterans has cancer of the lung developed up to the present? What percentage of these were gassed in the war? Is the percentage of gassed men significantly higher in the group with cancer of the lung than in the group without cancer of the lung? To these questions we have no exact answers, but we have the following data: Approximately 4,750,000 men were accepted by local draft boards. Of these, 740,000 were rejected at camps because of physical and mental defects. About 87,000 died of war injuries and disease, leaving approximately 3,923,000 men who survived the war. Of these, about 75,000 had been gassed and had survived. These figures are taken from the *Military Surgeon*, of October 1936,[23] and from Matz's[21] article on war gases. Thus about 1.9 per cent of the enlisted men were gassed and survived. If the death rate in the ensuing years has been about equal in the gassed and nongassed groups, we should expect that about 1.9 per cent of the surviving veterans have been gassed. If the death rate has been differential in the two groups, that figure will be higher if the gassed veterans have not died in such great numbers, and lower if they have died in larger numbers than the rest of the veterans.

Stein and Joslin[22] reported that of 164 veterans with cancer of the lung, 4.8 per cent gave a history of having been gassed. This would appear to be two and a half times the proportion of gassed men in the veterans' group in general. But if we calculate what departure from the average percentage of gassed men one might expect in so small a sample of veterans as a group of 164, we find that, on the one hand, no gassed men might be found, and, on the other, as many as 4.1 per cent might have been gassed without there being any causal relation between the gassing and the cancer. Therefore the 4.8 per cent found is not far removed from the 4.1 per cent expected, owing to variations in samples of veterans, and we can conclude that the difference is not enough to suggest that the gassing played any part in the production of cancer. Moreover, even if gassing were conceded to have induced cancer of the lung in some veterans, it would be obvious that most such cancers developed in veterans without previous gassing (95.2 per cent) and also that in most of the men who were gassed cancer of the lung has not developed—i. e., this lesion has appeared in only several hundred among a possible seventy-five thousand.

23. Griffith, C. M.: Mil. Surgeon **79**:251, 1936.

Occupations in Relation to Primary Cancer of the Lung.—Although many attempts have been made to link the occupation of the patient with his pulmonary cancer, these attempts have been unsuccessful with the sole exception of the pulmonary cancer which occurs in the miners of Schneeberg and Joachimsthal, in Bohemia, the incidence of which is so high in comparison with that of cancer of the lung in other places and so high in comparison with the incidence among the neighbors who are not working in the mines that there seems to be little doubt that this occupation is strongly productive of cancer of the lung. It is still a disputed point as to what the carcinogenic agent is in these mines. Arsenic, radioactive emanations and air-borne molds present in the mines have been implicated.

Outdoor occupations in which dust is inhaled have been thought to be represented unduly among the patients with pulmonary cancer (Duguid[24]); indoor occupations have been found to be represented in undue numbers (Bonser[25]). Industrial hazards (Schachter[26]), laboring jobs (Brockbank[27]), chromium dust (Alwens, Bauke and Jonas[28]), iron oxide in silica dust rather than the silica itself (Campbell[29]), silica dust (Anderson and Dible[30]; Dible[31]; Klotz[32]), metal grinding, exposure to coal gas in the air or to coal tar on the skin, and the preparation and sale of tobacco (the Kennaways[33]) have all been brought forward as possible causes of cancer of the lung. In all such instances the occupation given at the time the diagnosis of cancer is made may not have been the occupation of the patient at the time his cancer developed, perhaps twenty or twenty-five years before. Moreover, one must always take into consideration the district from which the data were drawn. Thus, in an agricultural district practically all the pulmonary cancers will be found in farmers, just as will most of the gastric cancers and most of the chronic nephritis. In a district where mining is the sole occupation most of the pulmonary cancers will be in miners. In districts where every one is working in tobacco, all the pulmonary cancers will be in tobacco workers, and so on. For any one district, the effect of occupation must be determined by finding the percentage of males of certain ages working in that occupation who

24. Duguid, J. B.: Lancet **2**:111, 1927.
25. Bonser, G. M.: J. Hyg. **28**:340, 1929; **34**:218, 1934.
26. Schachter, M.: J. de méd. de Paris **52**:700, 1932; abstracted, Am. J. Cancer **19**:165, 1933.
27. Brockbank, W.: Quart. J. Med. **1**:32, 1932.
28. Alwens, W.; Bauke, E. E., and Jonas, W.: Klin. Wchnschr. **15**:1854, 1936.
29. Campbell, J. A.: Brit. M. J. **1**:755, 1938.
30. Anderson, C. S., and Dible, J. H.: J. Hyg. **38**:185, 1938.
31. Dible, J. H.: Lancet **2**:982, 1934.
32. Klotz, M.: Am. J. Cancer **35**:38, 1939.
33. Kennaway, M. N., and Kennaway, E. L.: J. Hyg. **36**:236, 1936.

have pulmonary cancers, as compared with the percentage of males of the same ages not in that industry who have such cancers. One must not compare the incidence of cancer of the lung in middle-aged males working in mines with the incidence of cancer of the lung in all the rest of the villagers, males and females, of all ages. One must try to keep the two populations compared as constant as possible with respect to all factors with one exception, namely, the factor being investigated. Thus if one is attempting to ascertain the possible effect of dusty occupations on the incidence of pulmonary cancer, one must be sure that one deals with all those exposed to the same type of dust, on the one hand, and with those who do not meet that dust, on the other. Also, the distributions of the groups compared must be the same as to age and sex. Third, those exposed to the dust must not be meeting some other factor which might also theoretically be productive of pulmonary cancer, for example tobacco smoke. Even these simple rules are seldom followed in ascertaining the role of any occupation in determining the onset of cancer of the lung.

(*a*) Silicosis: Because of the fibrosis which occurs in the lungs of persons affected with silicosis, it has been suggested that this may have a role to play in producing cancer of the lung. The changes induced by silicosis are in the connective tissue rather than in the epithelium of the bronchus, and so it is not probable that silica will prove to be carcinogenic.

Silicosis was carefully looked for by Berblinger[34] in 50 cases of pulmonary cancer, and no evidence of it was found, although silicosis is very common in his district (Jena, Germany). That last clause changes the whole aspect of the finding. Had silicosis been rare in his district, his failure to find it would have given no indication of any possible lack of relation between the two. Hill[14] found no relation between silicosis and cancer of the lung in his cases or in reviewing the literature. If the cases of pulmonary cancer are in a district where there is a high incidence of silicosis, we should find the two occurring together with some frequency; if the cases are in a district where there is little silicosis, we should expect the two conditions to be associated seldom if they are not causally related. That the conclusions drawn from the incidence of these two diseases must be carefully controlled statistically is pointed out in an editorial in the *British Medical Journal*,[35] in a discussion of the cases of Anderson and Dible.[30] These authors found a high silica content in 12 of their 70 cases of pulmonary cancer, as compared with 48 cases used as controls. The editorial points out

34. Berblinger, W.: Med. Klin. **27**:1337, 1931; abstracted, Am. J. Cancer **16**: 839, 1932.

35. Silicosis and Pulmonary Carcinoma, editorial, Brit. M. J. **2**:411, 1938.

that even if their conclusion is correct, that silica plays a role in causing pulmonary cancer, the conclusion is not justified by the material they had. It goes on to say that such a conclusion would be justified only if there were a series of almost 3,000 controls, this figure being based on the incidence of primary cancer of the lung in the general population.

Klotz [32] found pulmonary cancer in 8 per cent of his series of 50 cases of silicosis, as contrasted with 1.17 per cent of 4,500 "unselected" autopsies which he used as controls. The latter group of autopsies were apparently on patients of 15 years and upward, as it did not include the autopsies of the pediatric service. The objection to conclusions based on such material is this: In using unselected autopsies, perhaps to obtain a so-called random sample, the control material was most dissimilar from the cases of silicosis under review. Among the subjects of unselected autopsies would be a large number of females, while the patients with silicosis would be entirely or almost entirely males. Cancer of the lung is most frequent in males; therefore one would expect to find more cases of cancer of the lung among patients with silicosis than among the subjects of autopsies in general merely on the basis of unequal sex distribution. Again, the patients with silicosis are for the most part in the middle age group or old age group, for it takes years for silicosis to develop. Cancer of the lung is most frequent after 40. The subjects of unselected autopsies will include many patients in age groups well below 40, an age at which cancer of the lung is infrequent. On the basis of age distribution we should expect to find more cases of cancer of the lung among patients with silicosis than among unselected subjects of autopsies. Finally, there will be variations in the percentage of cases of pulmonary cancer from group to group of autopsy cases, even when these groups are standardized for age and sex; these variations are attributable merely to the difference in samples of the population in each case.

It may be that Klotz's [32] conclusions are correct and that pulmonary cancer is more frequent among patients with silicosis than among a group similar in age and sex but without silicosis. But we must reject his conclusions as unsound until he has compared his silicotic patients with a group of men of the same age distribution as the patients with silicosis and made due allowance for possible variations between different samples of the population.

(*b*) Asbestosis: Few cases of asbestosis associated with primary cancer of the lung have been reported (Egbert and Geiger; [36] Hornig [37]). Here again we should expect to find the two conditions associated in the same person in some cases, on chance distribution alone. Since

36. Egbert, D. S., and Geiger, A. J.: Am. Rev. Tubere. **34**:143, 1936.
37. Hornig, F.: Ztschr. f. Krebsforsch. **47**:281, 1938.

asbestosis occurs in men of middle age, cancer of the lung may be found in these patients in a higher percentage than in the general population, but we have no proof that it is found in greater percentage when a group of men of similar age from the general population is used as the standard. The criticism that was made with respect to Klotz's data on silicosis may be made also of the data of Lynch and Smith.[38] Lynch and Smith have reported that in 2,343 consecutive necropsies over a period of twelve years cancer of the lung was found seven times, an incidence of 0.3 per cent. In the 35 cases of asbestosis, in some of which the lesions were very mild, cancer of the lung was found twice, an incidence of 5.7 per cent. Are these values significant, they asked, or is the sample of cases too small? Before such figures can be of any value, they must select from their 2,343 consecutive necropsy records only those on males, since their 35 cases of abestosis doubtless all relate to males. They must then select from these records on males only those on males in the age range of the males with asbestosis. When this is done, it will be easier to decide whether the incidence of pulmonary cancer is higher among patients with asbestosis than it is among those without asbestosis.

(*c*) Pneumonoconiosis: Other dusts besides silica are said to cause cancer of the lung. There may be much or little dust, depending on the occupations of the patients with cancer of the lung and on the district in which they live; rural patients will have little coal pigment, while residents of industrial cities like Pittsburgh will all have a great deal. South African miners have a high incidence of pneumonoconiosis but a low incidence of cancer of the lung.[2] Vorwald and Karr[39] examined the records of 15,587 persons who had long been exposed to dusty atmospheres and found that only 3 of them had cancer of the lung. He stated that the dust must be carcinogenic before its presence will induce cancer of the lung. Arkin and Wagner[40] and Berblinger[34] both found pneumonoconiosis rare in their series of cases of pulmonary carcinoma.

(*d*) Tarred Roads: Dusts and emanations from tarred roads have been said to be responsible for the increase of pulmonary cancer noted in the last two decades (Campbell[41]), but workers in Russia, where tarred roads are few, have noted the same increase in cancer of the lung as has occurred in other countries. Husted,[17] in Denmark, found that patients with primary cancer of the lung came in about the same proportion from areas where there were no tarred roads as from areas

38. Lynch, K. M., and Smith, W. A.: Am. J. Cancer **36**:567, 1939.

39. Vorwald, A. J., and Karr, J. W.: Am. J. Path. **14**:49, 1938.

40. Arkin, A., and Wagner, D. H.: J. A. M. A. **106**:587, 1936.

41. Campbell, J. A.: Lancet **1**:233, 1934; J. Indust. Hyg. & Toxicol. **19**:449, 1937.

where tarring had been carried out. Boyd [43] found no evidence that tarring had played any role in his 14 cases. Valade [42] pointed out that the conclusions which Campbell [41] reached as to the efficacy of this type of dust in causing cancer of the lung were based on the reactions of mice, which produce a high number of spontaneous pulmonary cancers, and that what might be carcinogenic for mice need not be so for men. We may conclude that there is no demonstrable proof at present that any form of dust has any role in producing cancer of the lung, for it has not been demonstrated that pneumonoconiosis is present in the lungs of patients with pulmonary cancer in any higher proportion than in a corresponding group of the general population.

Other agents, such as roentgen rays, tobacco smoke and motor exhaust fumes, have been suggested as possible causes. The suggestion that roentgen rays are a cause is almost absurd, for the probabilities are that only a small percentage of those in whom cancer of the lungs has developed ever had their chest under roentgen rays before they came for diagnosis of their cancer. Motor mechanics working in garages where there is an abundance of exhaust fumes are said to show no higher incidence of pulmonary cancer than the general population, and Campbell [43] stated that exhaust gases from internal combustion engines do *not increase pulmonary cancer in mice*. Tobacco smoke might be one factor in the increase of pulmonary cancer. The habit is one which permits long-continued application of the smoke to the bronchial mucosa; it is, or at least was, a habit more prevalent among men; there are two possible agents which might prove to be cancer producing, namely, heat and the derivatives of tobacco. There are those who point out that the increase in the consumption of tobacco parallels the increase in the incidence of pulmonary cancer. This may or may not have significance. If tobacco is a factor, it must be proved that derivatives of tobacco are carcinogenic or that the repeated application of heated smoke is conducive to cancer. McNally [44] stated that the tar in cigaret smoke contains enough chemical irritants to account for the increase in cancer of the lung. Roffo [45] found among a group of 5,000 cancerous women 42 who exhibited cancer in what he called the "smoke stream," namely, the lips, tongue, jaws, larynx and pharynx. All of these women were heavy smokers. He found that the products of burnt tobacco produced carcinoma when painted on rabbit ears, and he feels that there are probably many aromatic substances in tobacco that are carcinogenic. His findings are suggestive. But the increase

42. Valade, M. P., cited in Carcinogenesis in the Lung, Annotations, Lancet **1**:521, 1939.

43. Campbell, J. A.: Brit. J. Exper. Path. **17**:146, 1936.

44. McNally, W. D.: Am. J. Cancer **16**:1502, 1932.

45. Roffo, V. A. H.: Deutsche med. Wchnschr. **63**:1267, 1937.

in cancer of the lung should be much greater among females than among males, since smoking has increased among women far more rapidly in the last two decades than it has among men. Data published by the Metropolitan Life Insurance Company [46] show that the incidence is not greater among females. The rates among the industrial policyholders of 45 to 74 years of age show that in 1917 the rate for pulmonary cancer among females was 2.5 per hundred thousand. This rose to 8 per hundred thousand in 1938, an increase of 220 per cent. The rate for cancer of the lung in males rose in the same period from 3.2 to almost 23 per hundred thousand, an increase of more than 600 per cent. Their conclusion is that it appears doubtful that smoking is a factor in causing cancer of the lung.

Controlled observations over a longer period are necessary to settle this point. Investigators must not rest content with finding that a high percentage of patients with pulmonary cancer are tobacco smokers; they must find that the percentage of smokers in this group is significantly higher than that in the general population of a similar age and sex distribution.

When we review all the theories on the cause of pulmonary cancer, we find that not one supposed cause has been *proved* to be a real cause and that none of the alleged causes has been investigated with sufficient statistical accuracy to enable the observer to pass an opinion carrying any weight. No one cause, no sum of causes, no common factor in them, namely, chronic irritation through inflammation of the bronchial mucosa, has been demonstrated to occur with any greater frequency in patients with cancer of the lung than in a group from the general population of comparable age and sex distribution at a time sufficiently long before the onset of the cancer that it may be interpreted as antedating this rather than following it. Naturally, any condition which is a sequela of cancer of the lung may be found more frequently in patients with pulmonary cancer than in persons not affected with this type of cancer. Such a condition when obviously the result of cancer of the lung must be excluded from a discussion of the latter's causes.

(*c*) Schneeberg Miners: The high frequency of cancer of the lung among the miners of the Schneeberg and Joachimsthal valleys has been recognized for many years. It seems that this occupation is one which does enhance the incidence of pulmonary cancer beyond that known elsewhere and apparently beyond that of the neighbors of the valleys who do not work in the mines. Thus Pirchan and Sikl [47] stated that 12 of 19 Schneeberg miners dying in 1929-1930 had cancer of the lung at autopsy. Of 12 miners dying in 1932, 9 had a *clinical* diagnosis of

46. Cancer of the Lung a Growing Health Problem, Statist. Bull. Metrop. Life Ins. Co. **20**:7, 1939.

47. Pirchan, A., and Sikl, H.: Am. J. Cancer **16**:681, 1932.

pulmonary cancer. Sikl [48] reported similar figures for the miners of Joachimsthal. Of 15 miners dying in eighteen months, autopsies were carried out on 10; of these, 8 had carcinoma of the lung. The average age of these men was 49, and the average period of exposure in the mines was seventeen years. This incidence of cancer of the lung has not been equaled anywhere else in the world. The cobalt, the arsenic, the dust, the radioactive emanations all have been incriminated. Sikl [48] stated that chemical analysis of the lungs showed no trace of important foreign elements. The test for radioactivity was negative, although he felt that radioactive emanations in the mines may have a part in producing pulmonary cancer. Maisin [49] quoted de Laet as saying that in Belgium pulmonary cancer has not developed in workers in radium although they wear no masks and are covered with and breathe the dust of the works all the time. However, the plant had been in operation only twelve years at the time of de Laet's report.

Of interest in this connection are Martland's [50] findings in workers with radium paint. The girls who died of osteogenic sarcoma were exhaling radioactive air, as shown by tests, yet none of them presented cancer of the lung. A whole series of questions to which we have as yet no answers, and may never have, arise. If the radioactive emanations in the air in the Schneeberg mines are responsible for cancer of the lung, why did the radium paint workers in the United States die of bone and not lung tumors, especially as it was shown that the lungs were exposed to radioactive emanations? May it be that there is an inherited factor for cancer of the lung in the Schneeberg miners which has been increased through long-continued inbreeding in these rather isolated mountain valleys with a small population and that the carcinogenic agent in the mines (whatever it may be) enhances an already present tendency toward pulmonary cancer? Is it possible that, taken in small doses, the radioactive substance induces pulmonary cancer, which may have a long latent period, whereas radium taken in presumably larger quantities, as is the case when radium paint is swallowed, may induce bone tumors, with a shorter latent period of development? Thus these victims would die of osteogenic sarcoma before they had time to develop pulmonary cancers. Certain it is that although the miners have a very high incidence of cancer of the lung they do not have a high incidence of those chronic pulmonary conditions which are supposed to predispose to cancer of the lung. Thus Pirchan and Sikl [47] said that of the 9 men with clinically diagnosed cancer of the lung, not one had a history of chronic pulmonary disease that was not directly related to the onset of the cancer.

48. Sikl, H.: Ztschr. f. Krebsforsch. **32**:609, 1930.

49. Maisin, J.: Cancer, Bruxelles **11**:111, 1934; abstracted, Am. J. Cancer **28**: 164, 1936.

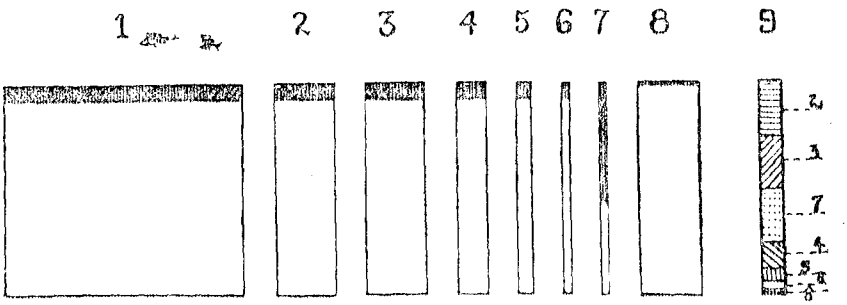
50. Martland, H. S.: Am. J. Cancer **15**:2435, 1931.

Throughout this discussion we have repeatedly emphasized that it makes no difference how great is the percentage of patients with cancer of the lung who point to any particular disease in their past history, provided that a similarly great percentage of the general population has had the same disease. Thus if the cancerous patients come from a region in which the whole population has had measles, every patient with cancer of the lung will give a history of measles. If 90 per cent of the population past 40 have had tuberculosis, 90 per cent of the patients with cancer of the lung will probably give a history of tuberculosis. If the main occupation in the district is farming, most of the patients with cancer of the lung will be farmers, but if mining is the main industry, most of the patients with cancer of the lung will be miners. This fact has been little appreciated by those who argue that because 25 or 50 or 75 per cent of patients with cancer of the lung give a history of a particular disease that disease must be carcinogenic; hence we shall try to present this matter more in detail at this point.

In the accompanying chart the first rectangle represents a theoretic population. One fourteenth of them (black bar at the top) is characterized by having a certain disease, X. The subsequent rectangles represent those portions of the population which have had some other condition. Thus in rectangle 2 we might indicate those who had had, for example, chronic bronchitis; in 3 those who had had influenza; in 4, those with arteriosclerosis, and so on. We will assume that none of these groups overlap. Now it will be seen that one fourteenth of the population in rectangle 2 also has disease X, the same proportion as was present in the general population. This is true of the groups represented in rectangles 2 to 6. The group in 7 shows a much higher concentration of X patients than do the other groups, while the group in 8 has fewer X patients than has the general population. From such a diagram one would be justified in looking on the group in 7 as probably peculiarly susceptible to disease X, while those in 8 would be considered relatively immune. We are assuming in this example that all the groups are comparable as far as sex, age and other significant factors are concerned.

Now let us arrange these same data in rectangle 9, which represents the population affected with X, which is one fourteenth of the total population. Here we see that three groups each have a fourth of the patients with disease X. These are 2, 3 and 7. Group 4 has an eighth; group 5, one sixteenth, and groups 6 and 8, each a thirty second of all X patients. If we looked at this column without viewing the data in columns 1 to 8, we should be very likely to conclude that groups 2, 3 and 7 are equally susceptible to X and that groups 6 and 8 are the most immune to this disease. The latter conclusions would, of course, be wrong, as the data in the rest of the diagram clearly show.

It is in the latter form that the data dealing with the cause of pulmonary cancer are usually presented. We are told that a certain percentage of patients with cancer of the lung give a history of chronic bronchitis or of influenza or of some other condition, and if this percentage is high, it is assumed that the disease named is an important



1. The general population is represented in rectangle 1. Those with a history of a disease which we will call X are shown by the black bar at the top. This is one fourteenth of the total area of rectangle 1. All percentages in this figure are of course theoretic and are used merely for purposes of demonstration.

2. This rectangle represents the proportion of the total population, namely, 25 per cent, which has had chronic bronchitis. Note that one fourteenth of this group also have X.

3. This rectangle represents those in the population, namely, 25 per cent, who have had influenza. One fourteenth of them have X.

4. This rectangle represents those in the population who have arteriosclerosis, namely, 12.5 per cent. One fourteenth of them have X.

5. This represents the part of the population which has asthma, namely, 6.25 per cent. One fourteenth of them have X.

6. This represents the part of the population with a history of war gassing, namely, 3.12 per cent. One fourteenth of them have X. Because X has developed in the five groups 2 to 6 in the same proportion as in the general population, we cannot assign a specific role to any of these conditions in the production of disease X.

7. This is the part of the population who are miners of radioactive ores, namely, 3.12 per cent. Here the incidence of X is eight times as great as that found in the general population or in the five preceding groups of the population. It appears that some factor associated with mining of these ores is productive of X. But because not all miners have X, and because many who are not miners do have X, other factors besides the mining of these ores enter into the cause of X.

8. This is the part of the population which has a history of tuberculosis, namely, 25 per cent. The incidence of X is much lower here than in the general population, as if some factor inhibiting the development of X was present in this group.

9. This rectangle shows the part of the population in which X develops. One fourth of these have had bronchitis, another fourth influenza, another fourth exposure to radioactive ores. One eighth have arteriosclerosis, one sixteenth have asthma, one thirty-second have had tuberculosis, and one thirty-second have been war-gassed. Data in the latter form are usually used to determine the importance of any specific disease as a cause of cancer of the lung. It is assumed that all the groups in the rectangles 1 to 9 are of the same age and sex distribution and that no group in any rectangle overlaps that in any other.

causative factor in producing carcinoma of the lung. If the percentage is low, it is assumed that the disease has no significance in the causation of cancer of the lung. The diagram in figure 1 shows that it is only when the disease in question is found in a much higher percentage of the group with pulmonary cancer than of the general population that one can consider that it has an etiologic role in producing pulmonary cancer.

But even this is not enough. It is necessary that the group in the general population which we are using as a control for the pulmonary cancer population be comparable to the latter in all respects except that the general group does not have cancer of the lung; otherwise one might find that the group with cancer of the lung had the condition in question in a higher percentage than had the general population without there being any significance in that fact. For example, some of the veterans of the World War are asking for compensation for cancer of the lung, which they claim was brought on by the chronic pulmonary diseases which they contracted through exposure encountered during military service. Now how might one go about settling the justice of such a claim? One might say, "The incidence of pulmonary cancer among war veterans is much higher than among the general population, therefore it must have been the hardships of military service which caused this increase." (We are assuming for the sake of the argument that it is more frequent among war veterans.) But the war veterans are all males, and the general population holds more females than males. Hence an adjustment for sex would have to be made so as to make both groups comparable. Next, the average age of the war veterans lies between 45 and 60, while the age of the general population will range all the way from birth to 100 years. The two groups must be made comparable as far as age is concerned. Then one might argue that although the hardships of military service did not actually cause pulmonary cancers they caused these lesions to develop much earlier, because the age at which the cancers were developing in the veterans was much younger than that of the patients with such cancers in the general population. But again the age distributions in the two groups are different, the ages of the veterans being concentrated in the range from 45 to 60, while the general population has those under 45, among whom pulmonary cancer is not frequent, and those from 60 on, among whom it is frequent. Hence only those among the veterans who were destined to get cancer of the lung at younger ages would be included in the veteran group. Those in whom it will develop after 60 are not included, since the veterans have not yet reached 60 years and over. In this way the average age at which pulmonary cancer developed in the veterans would be less than that at which it develops in the general population.

SUPPOSED ENVIRONMENTAL FACTORS: A GENERAL DISCUSSION

The introduction of a consideration of experimental work into a discussion of carcinoma of the human lung may seem irrelevant, but it is not really so. For a few decades the experimental production of carcinoma by so-called chronic irritants lent strong confirmation to the idea that chronic irritation was the sine qua non of all cancer. Thus when no evident chronic irritant was found, it was assumed that it was present anyway, as witness the citations at the beginning of the paper. The evident irritants were mechanical, thermal, chemical and bacteriologic agents. Sometimes it was stated that it was not the irritant but the chronic inflammatory changes set up by it that produced the cancer. In recent times, however, we have come to look on carcinogens as involving more *specific* agents. Certain viruses, such as that of Rous, have been shown to be the cause of certain definite animal tumors. Specific chemical bodies, such as dibenzanthracene and the estrogens, have been shown to produce carcinoma on repeated application. Much depends, apparently, on the chemical formula; comparatively minor alterations in the structure of the compound mean wide alterations in the carcinogenic power. A large literature has grown up around these carcinogens (Cook,[51] Andervont [52] and others).

It has been found experimentally that not all chronic irritants produce cancer and that some of the highly carcinogenic agents are not irritating, that what may be carcinogenic for one animal need not be for another animal or even in another strain of the same animal, and finally that what is carcinogenic for one organ in an animal need not be productive of cancer in another organ of the same animal.

Let us illustrate these points briefly. Some marked irritants, such as mustard gas, are not cancer producing although they cause intense inflammatory reactions (Visser and ten Seldam [53]). Again some highly carcinogenic chemicals are nonirritating when applied to the skin (Andervont [52]). Tar painted on the skin of rats did not produce cancer of the skin, while if painted on mice or rabbits it did cause such cancer. The same tar painted on mice differing in their genetic susceptibility produced cancer of the skin in highly susceptible mice and failed to produce cancer in highly resistant mice (Kreyberg [54]). It is of interest

51. Cook, J. W.: Proc. Roy. Soc., London, s.B **111**:485, 1932.

52. Andervont, H. B.: Effect of Bacterial Products on Growth of Malignant Tumors, in A Symposium on Cancer, Madison, Wis., University of Wisconsin Press, 1938, p. 54.

53. Visser, J., and ten Seldam, R. E. J.: Geneesk. tijdschr. v. Nederl.-Indië **77**:3092, 1937.

54. Kreyberg, L.: Genetic and Constitutional Aspects of Spontaneous and Induced Tumors, in A Symposium on Cancer, Madison, Wis., University of Wisconsin Press, 1938, p. 183.

that cotton mule spinners suffer from cutaneous cancer due to the constant spraying of the skin with liquid petrolatum, whereas they do not exhibit cancer of the lung in any increased percentage although they constantly inhale air in which the same oil is present in the form of fine spray (Simpson[55]). Chimney sweepers had a high percentage of cancer of the skin, yet the constant inhalation of an atmosphere containing the same carbon particles as caused cutaneous cancer did not lead to cancer of the lung. Injections of estrogens are productive of cancer of the breast and of the uterus in mice but not of cancer of the gastrointestinal tract or of the lung.

Therefore it can be stated that before any condition, such as chronic pulmonary disease, can be regarded as producing cancer it must be proved beyond doubt that (1) the condition is capable of producing cancer apart from any ability to cause chronic inflammatory change, (2) that it is capable of producing cancer in the animal under discussion and (3) that it is capable of producing cancer in the specific organ in question. Merely to show that a condition induces chronic inflammatory changes in an organ is no longer sufficient, for it is known that chronic inflammatory changes can exist for long periods without producing cancer and also that cancer can occur with no reasonable evidence of preceding inflammation—for instance, in retinal blastoma shortly after birth.

PROBABLE ROLE OF HEREDITY IN PULMONARY CANCER

Although specific carcinogens can produce cancerous changes, are the conditions mentioned earlier in the paper shown to be carcinogenic? It has been assumed that they may be because one has no other explanation of pulmonary cancer if one insists on the presence of extrinsic factors as the sole causative agents of all cancers. But cancer is a problem of failure of differentiation, of organization and of growth; differentiation, organization and growth are problems of the inherent makeup of the cell itself and of its ability to utilize certain chemicals in its metabolic processes. Therefore one should not overlook the fact that "idiopathic" alterations in the inherent makeup of the cell may be responsible for cancerous changes without the intervention of any carcinogenic agent. In other words, the cancer may arise through hereditary causes. It is known that under the influence of hereditary determiners descendant cells of the original zygote differentiate into cells with quite widely differing potentialities. Absence or alteration of these determiners for normal differentiation may also be hereditary. Thus the alterations necessary for changing a normal cell into a cancer cell may be under the aegis of determiners located in the germ plasm.

55. Simpson, S. L.: Quart. J. Med. **22**:413, 1929.

This alteration sui generis may come about through two different mechanisms. One may be a somatic mutation, i. e., a sudden departure from the normal line of cells from which the altered cell sprang, which departure then becomes hereditary for all cells descended from that original mutating cell. That such a mutation should occur would be wholly unexpected, since there was no factor in the original fertilized germ cell from which the individual came which played a role in determining the occurrence of the mutation. The patient with cancer of the lung in this case would not have come from a strain in which factors in cancer of the lung were inherited, nor would he be liable to have more offspring in whom cancer of the lung would develop than a person without cancer of the lung.

The second mechanism would be one in which the tendency to alter into a cancerous cell would have been inherited, being due to factors resident in the fertilized germ cell. Just as there are inherited factors which guide the destiny of the entodermal cells which form gut, then bile duct, then liver, so that this development proceeds normally in an orderly fashion at definite times in the life of the embryo, the times differing depending on whether the embryo comes from a mouse, a dog or a human ovum, and just as there are inherited factors which permit cartilaginous development at the epiphysial lines for so many years in the human humerus but for a different number of years in the femur before the cartilage cells cease proliferating and allow bone growth to cease, so there may be inherited factors which permit cells in a specific location at a specific time in the life history of the individual to alter and become cancer cells.

What proof have we that these last two mechanisms are possible and that not all cancer nor indeed all pulmonary cancer needs be interpreted as arising through the agency of extrinsic carcinogenic factors? First, with the single exception of the pulmonary cancer of the Schneeberg and Joachimsthal miners, we have no adequate proof that cancer of the lung in man is caused by extrinsic factors. This is negative evidence, but it should be of value in forcing us to hunt for other causes of human pulmonary cancer before we accept all pulmonary cancer as being due to external agents. For the idea that sporadic somatic mutations or hereditary alterations are frequently the cause of cancer of the human lung we have the following indirect additional evidence. The vast majority of such cancers in man appear to rise from one point of origin, as would be expected were a somatic mutation the cause, whereas if external agents acting on the lung were responsible we should expect that the tumors would be multiple and over both lungs. Thus tumors induced in mice by hydrocarbons are not bronchiogenic as in man, but subpleural, and may be multiple rather than

single, and may be bilateral. Second, we know that mutations do occur in the germ cells and that the cells with such mutations are then propagated as a new line of individuals. There is no reason to suppose that mutations are limited to germ cells alone and that such mutations could not occur in any somatic cell in the body.

Have we any evidence that definite hereditary factors may be present in the germ cell which cause cancer of the lung to appear at a definite time in the life cycle of the individual? As far as cancer of the lung is concerned we have no human pedigrees that would prove it to be inherited, and again the evidence must be indirect. Cancerous alterations of cells have been found to be inherited in strains of mammals in which experimentation is possible. The type of cancer produced by the strain is more or less constant. Thus there are strains with a high incidence of pulmonary tumors (Lynch[56]), others with a high incidence of mammary tumors and others with a high incidence of hepatic tumors. There are strains of mice in which several types of tumors may be capable of developing but which tend to die of the type developing first, thus obscuring the other cancerous potentialities. Since man biologically is much more closely *identified with* other mammals than he is *differentiated from* them, it would be reasonable to suppose that if cancer shows dependence on hereditary factors in mice the same will be true for man, although the actual mode of inheritance may differ widely in the two species.

In rectal, gastric, mammary and uterine cancer in man we see good evidence that related members of a family tend to resemble each other more closely in the production of these tumors at a definite time in their life than do unrelated members of a community (Macklin[57a]). This suggests that hereditary factors play a predominant role in many if not in all of these tumors. Cancer of the lung was seldom recognized before 1900. Hence, even if it were inherited and transmitted according to a simple scheme so that one would frequently encounter familial cases, we should not have many records of familial instances, owing to the fact that pulmonary cancers in the preceding generations remained undiagnosed.

Finally, we may use the evidence furnished by tumors in twins (Macklin[57b]). True we have no records of pulmonary cancers in twins, but since cancer of the lung is like all other cancers except that it occurs in the lungs instead of elsewhere, we may not be assuming too much when we use tumors in twins to show that cancer and hence pulmonary cancer may be inherited. If one examines records of can-

56. Lynch, C. J.: J. Exper. Med. **54**:747, 1931.

57. Macklin, M. T.: (*a*) Familial Incidence of Cancer, in a Symposium on Cancer, Madison, Wis., University of Wisconsin Press, 1938, p. 32; (*b*) J. Heredity **31**:277, 1940.

cers in monozygotic and dizygotic twins, one finds the following facts: Monozygotic twins, with an identical inheritance, resemble each other far more often in both having a cancer and having it in the same organ and at about the same time of life than do dizygotic twins, who may have with respect to cancer either an identical or a different heredity. This is true even when the dizygotic twins studied are all of the same sex, thus eliminating differences in environment due to occupation which are present when the twins are of the opposite sex. This would indicate that although somatic mutations may be responsible for some cancers they are probably not responsible for all, for it would be very rare for identical twins to have an identical somatic mutation in the same organ at about the same age were that mutation not under the guiding influence of heredity.

To sum up, then, it would seem that the so-called chronic irritants supposed to be responsible for cancer of the lung have not been proved to be causes of such cancer, since (1) many have cancer of the lung who are not exposed to these chronic irritants, while (2) many exposed to them never have cancer of the lung. Until such proof is forthcoming, investigators are closing their minds to other, perhaps fruitful possibilities by insisting that because specific carcinogens are responsible for cancer of the lung in some instances they must be in all. Such an attitude is no more reasonable than to state that because diabetes develops in an animal from which the pancreas has been removed, all diabetics are without a pancreas. Sporadic mutations and hereditary influences may and most probably do play a large role in causing pulmonary cancers as well as other types of malignant growth.

SUMMARY

In conclusion, then, we may say that none of the specific diseases or conditions causing chronic inflammation of the lungs can be said to have been proved to be causes of cancer of the lung. They have not been shown to be more common in patients with pulmonary cancer than in a group of the general population of similar age and sex, and until a *significant* difference can be found between their incidence in those with pulmonary cancer as compared with those without pulmonary cancer their causal relation to this type of cancer will remain purely speculative. This, of course, refers to chronic inflammatory diseases which have antedated the cancer by a sufficient number of years so that they can be excluded from being interpreted as the result, not the cause, of the cancer.

Chronic irritation, especially in the form of chronic inflammatory disease, as a cause of pulmonary cancer has been assumed; the idea has been copied from text to text, repeated from author to author, with

little critical analysis of its possible role. Somatic mutations and hereditary factors must be considered and their probable role in causing cancer of the lung recognized. True carcinogenic agents for the production of cancer of the lung will no doubt be found as modern industry expands its use of chemicals. But, as some types of cancer will develop in one seventh of men over 40 and since about one fifth of all cancers in males are in the lungs, one thirty-fifth, or about 3 per cent, of all men over 40 will die of this type of cancer. There may be an increase in the incidence of cancer of the lung in any industry beyond the maximal rate for cancer of the lung in the general population, but one can never state that any patient would not have had cancer of the lung had he not been in that occupation. Thus even with the presence of carcinogenic agents admitted, their role in causing cancer of the lung cannot be proved in any individual case, nor can they be said to be 100 per cent effective, since a certain percentage of persons exposed to the carcinogenic agents would have had pulmonary carcinoma even without this exposure. The effectiveness of any carcinogenic agent in producing carcinoma of the lung can be judged only by the *increment of increase* of carcinoma of the lung in large groups, *not by its total incidence*. It is therefore impossible to assign to any extrinsic factor an absolute role in carcinogenesis in any individual case.

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