A Brief Discussion of the Etiology of Bronchiogenic Carcinoma

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It is a high honor which I greatly appreciate to be invited to give the first Jacob Jesse Singer lecture before the American College of Chest Physicians. A close association of approximately 20 years with him gave me the opportunity to recognize his many fine qualities. It was a great shock to me when I received the news that he had been suddenly struck down a few months ago. However, his friends can all be glad that before his death he knew that this lectureship had been established in his honor.

My first acquaintance with him was in the fall of 1919 after my discharge from the army when I went to St. Louis to become the Bixby Professor of Surgery at Washington University. My interest in the future possibilities of chest surgery had been aroused by my connection with the Empyema Commission during World War I. I found Jack to be greatly interested in what we had done and to be particularly well acquainted with the experimental work on pneumothorax which Bell and I had carried out while members of the Commission. He had already begun to specialize in the diagnosis and medical treatment of chest diseases and we naturally fell together as a sort of sympathetic team.

Soon it became evident that it would be desirable for us to have some space in the Barnes Hospital where we could examine patients with a fluoroscope and have daily conferences with each other, with members of the house staff and with such students as cared to attend. We began in some old storage quarters on the second floor which Jack persuaded the superintendent to let us have. We installed a fluoroscope and other equipment and began functioning in the fall of 1920 as a so-called Chest Service. Our conferences became daily occurrences every afternoon—at first for about an hour, and later becoming lengthened to two or three hours. Almost at once we were faced with the problem of an inability to accommodate the number of visitors who wanted to come—not only students and others from our own institutions but from out of town as well.

It was a great personal loss to me when Jack made the decision to go to Los Angeles but fortunately we were able to keep up our friendship

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357
By correspondence and by seeing each other at meetings of the American Association for Thoracic Surgery of which he was a long-time and much interested member.

During the days of high mortalities in chest surgery it was a great comfort to me to have Jack's support. At times also he put the brakes on me. The conservatism which he expressed on those occasions, although sometimes resented by me, was probably good for both of us. The younger chest surgeons of today cannot possibly appreciate the criticism both open and veiled which the internists had in the 1920's for those of us who were trying to develop chest surgery. It seemed to be the general opinion of the medical men that to refer a patient to a chest surgeon was the equivalent of notifying St. Peter to expect a new arrival. It required courage for Jack to give me his support during those dark days, for he undoubtedly lost caste among his confreres by doing so. I am glad to make this expression of appreciation even if it is posthumous.

Jack Singer had a gift for things mechanical. Working on his pneumothorax apparatus gave him a great thrill; and when the final model was completed he felt a great satisfaction. It was undoubtedly the most efficient and the simplest to use of any of the apparatuses of the time. His supraglottic aspiration method of using lipiodol for bronchography was a very important addition to our diagnostic armamentarium and unquestionably its invention, by supplanting more cumbersome and even dangerous methods, did much to popularize the use of bronchography.

Now to get to the subject matter of the lecture.

With the exception of a very few die-hards, who refuse to admit the evidence, almost everyone agrees that bronchiogenic cancer, or primary cancer of the lung, has shown a remarkable increase in its incidence during the last 25 years. For example, the vital statistics of the U. S. Public Health Service show that in 1930 the deaths from the condition in men were less than those from cancer of the skin, of the liver, of the rectum, the intestine, the prostate and the stomach. By 1950, however, the most recent year when the statistics are available, bronchiogenic cancer had taken first place in the cancers affecting the male sex, and, from all that is known, the increase is progressing. The incidence of most of the other cancers has shown practically a straight line during the 20 years.

This astonishing increase in the incidence of lung cancer during a short period constitutes a most remarkable phenomenon which apparently is unique in the history of cancer. It behooves everybody, therefore, who is interested in this disease to try to find an explanation.

One other remarkable fact about bronchiogenic carcinoma is that it occurs much more frequently in the male sex. There is a considerable difference in the published statistics of the sexual ratio. Probably about an average ratio would be six males to one female.

Since the rapid increase of this disorder has roughly paralleled the rapid increase in the use of motor vehicles, it was only natural to suspect that perhaps the explanation might lie in the general exposure to some possible carcinogen connected with the automobile. However, in a study of 857 cases of bronchiogenic carcinoma by Wynder and myself (1951) with
special reference to industrial exposures as possible etiological factors, we
found no significant increase of this cancer in garage men, automobile
mechanics, chauffeurs and oil-field workers. There are, nevertheless, cer-
tain other occupations which carry with them increased risks of develop-
ing the condition. Probably the most striking examples were brought out
in the well-known studies made on the Schneeburg and Joachimsthal miners
with incidences of 40 per cent and 48 per cent respectively of deaths from
lung cancer in the two places. The interested reader may find an excellent
review of the occurrence of the disorder among those miners in the article
by Lorenz (1944). More recently the chromate industry has been found
to be associated with a higher incidence of lung cancer than the general
population. This association has been well described by Mancuso and
Hueper (1951). However, one can hardly blame such industrial associa-
tions for the tremendous increase in incidence of the disease because of
the relative insignificance of the numbers engaged in those industries.
Kotin has recently discovered some carcinogens in the atmospheric smog
of Los Angeles. But it would be difficult to incriminate atmospheric pol-
lution for the widespread increase of bronchiogenic carcinoma because if
that were a responsible factor women undoubtedly would be victims of the
disease as often as men. Moreover, as Peacock of Glasgow has informed
me, there are analyses of the atmosphere of that city which were made
a century ago that show practically the same composition as today. It
would seem therefore that if atmospheric pollution is an important etio-

FIGURE 1: Death rates for selected respiratory diseases and sites of cancer among
white males, United States 1930-50. (Rates standardized for age on the 1940 popula-
tion.) The chart shows the rapid rise in the curve of incidence of cancer of the res-
piratory system in comparison with the nearly straight lines of other common cancers.
(Prepared by Dr. E. Cuyler Hammond, chief statistician of American Cancer Society,
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logic factor there would not have occurred the same recent great increase in the incidence of lung cancer in Glasgow that has been noted elsewhere in Great Britain and in the United States.

Another possible etiologic factor that has been suggested frequently is tobacco smoking. This suggestion was made as long ago as 1912 by Adler who wrote the first monograph on primary lung cancer at a time when the condition was still rare. Brosch in 1900 had made some unsuccessful attempts to produce cancer experimentally in guinea pigs by painting them with tobacco "juice." The list of additional writers who since then have mentioned smoking as a possible factor is a long one. Most of them, however, were content to make the suggestion and did nothing further to find out. However, a few submitted their idea to experimental studies, but the experiments were not conducted for a long enough time and in some instances the method of study is not reported in sufficient detail to make the results satisfactory. For example, Hoffmann and his associates painted their animals (mice) for only 14 days, a very inadequate length of time, but they did observe hair loss. Wacker and Schmincke noted epithelial proliferation in rabbits' ears 21 days after a subcutaneous injection of pipe tar. Lorenz and his co-workers failed to obtain pulmonary

![Bar chart showing the amount of cigarette-smoking in 605 male patients with proved bronchiogenic carcinoma as compared with 780 males over 35 years of age without cancer of the lung (Wynder and Graham 1950). The arbitrary classifications of smoking are as follows: Non-smokers (less than one cigarette per day for more than 20 years); light smokers (up to one-half pack per day for more than 20 years); moderately heavy (one-half to three-quarters of a pack); heavy smokers (three quarters to a whole pack); excessive smokers (one to one and three quarters packs); chain smokers (more than one and three quarters packs).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21261/ on 06/26/2017)
tumors in mice which were made to inhale tobacco smoke. The literature on the attempts to produce cancer experimentally has been summarized in an article by Wynder, Graham and Croninger (1954). Ochsner and DeBakey in 1941 called attention to the similarity of the curve of the increased sales of cigarettes in this country to the greater prevalence of primary cancer of the lungs and concluded from those curves that there is a possible etiologic relationship between cigarette smoking and bronchiogenic carcinoma.

In spite of sporadic suggestions of an etiologic relationship and a few experimental attempts to produce cancer with tobacco products no large scale study was undertaken to try to determine such a possibility until 1949 when Wynder and the writer began theirs. In May, 1950, that study was published. It was based on 684 proved cases of bronchiogenic carcinoma. Nearly all the patients were in the Barnes Hospital, St. Louis, but the sampling was not restricted to a small locale since the patients came from many places in the Middle West and Southwest of the United States. They were interviewed about their smoking habits by one of two non-medical young women who used a standard questionnaire which had been devised by us. The study brought out the fact that of 605 men with bronchiogenic carcinoma, other than adenocarcinoma, no less than 86.5 per cent had smoked from about a pack to more than two packs of cigarettes a day for at least 20 years; and among those men with the two com-

![Figure 3: This chart shows to be false the common idea that women smoke as much as men. The statistics were obtained by questioning 780 male and 552 female patients in the Barnes Hospital. None of the patients had a bronchial carcinoma and all were more than 35 years old.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21261/)
mon types of carcinoma (epidermoid and undifferentiated) only 1.3 per cent were non-smokers. Of a control group of 780 men without lung cancer 54.7 per cent had a similar history of heavy smoking of cigarettes but as many as 14.9 per cent were non-smokers. Another important finding was that no less than 72 per cent of the lung cancer patients stated that they had smoked from 30 to 50 years. Our study also showed to be erroneous the current opinion that women smoke as much as or more than men. Of 552 women patients without lung cancer and above the age of 35, in the Barnes Hospital, no less than 79.6 per cent of them were non-smokers, as compared with only 14.9 per cent of men in a similar group. It is the young women and the girls, rather than the women of the cancer age, who do the heavy smoking. Moreover, they are too young to have smoked the necessary time to develop a lung cancer, 25 years or so.

Our results were strikingly confirmed by the publication in September, 1950, of the now well-known statistical study of Doll and Hill in England. Their study was being made at the same time as ours, but we happened to precede them in publication by a few months. It was based on about the same number of patients as ours. Of 649 men with lung cancer they found only 0.3 per cent of non-smokers, compared with our figure of 1.3 per cent. As in our series Doll and Hill found that a high percentage of the men with cancer were heavy cigarette smokers. They concluded that their findings “suggest that, above the age of 45, the risk of developing the disease increases in simple proportion with the amount smoked, and that it may be approximately 50 times as great among those who smoke 25 or more cigarettes a day as among non-smokers.”

In addition to our own and that of Doll and Hill there have been 10 other statistical studies reported, making 12 in all (Dungal 1950, Levin et al. 1950, Mills and Porter 1950, Schrek et al. 1950, Gsell 1951, McConnell et al. 1952, Kououmies 1953, Sadowsky et al. 1953, Wynder and Cornfield 1953 and Breslow et al. 1954). The results of all of the 12 studies have been essentially the same. They have all shown that cancer of the lung occurs nearly always in heavy cigarette smokers. It is very significant that no study has been reported which gives any different conclusion. The skeptics should ponder that fact.

The general agreement among all the statistical studies is very strong evidence in itself that there is a definite etiologic relationship between excessive cigarette smoking and cancer of the lung. Yet obviously that relationship would seem to be more definitely established if cancer could be produced experimentally by the use of cigarette smoke. Earlier in this article brief mention has been made of a few of the experimental attempts using various tobacco products. The literature pertaining to this earlier work has been summarized in an article by Wynder, Croninger and myself published in 1953. For the most part the results have been negative, although a total of seven epidermoid cancers of the skin have been reported as having been obtained in mice with products of cigarette smoke out of many animals used. Most workers who have attempted to cause experimental cancer with tobacco products have used rabbits. Roffo (1939) reported the successful production of carcinoma in rabbit ears after paint-
ing them with a distillate of tobacco, but Sugiura failed in his attempt to reproduce Roffo's results. Also Flory (1941) succeeded in obtaining only what he called "carcinomatoids" in rabbit ears after application of a tobacco distillate.

It seemed therefore that the actual experimental production of carcinoma by the use of tobacco products had been so rare that a doubt could be raised that in any instance an etiologic relationship had been established. On the basis of that conclusion we decided to undertake some experiments to determine if cancer could be produced by the use of tar from cigarette smoke. It seemed to us highly desirable, if possible, to bring some experimental evidence to this controversial subject, in addition to the statistical evidence. An especially important point was to use a proper strain of mice which is known not to develop spontaneous cancers of the skin. In the study therefore we used the inbred strain known as CAF1, that was developed in Dr. C. C. Little's laboratory at Bar Harbor, Maine, and that is known to be free from spontaneous tumors of the skin.

A machine was devised by which, with a small electric motor, we smoked 60 cigarettes at a time. The smoke was collected in flasks cooled by dry ice. The sudden chilling of the smoke precipitated the tar from it which was dissolved in acetone. The acetone solution was painted on the skin of the mice* three times a week, after it had been evaporated to a composition of equal parts of tar and acetone. Control mice painted with acetone alone showed no reaction of the skin whatever—not even any evidence of irritation.

Papillomas appeared in 59 per cent (26 females and 22 males) of 81 tarred CAF1 mice. Although 8.6 per cent of the papillomas regressed, no less than 44.4 per cent (or 36 mice) developed epidermoid cancer of the skin. Sometimes there were two cancers in one mouse and in one case there were three, but in most instances only one cancer appeared in the painted area. In view of the much greater frequency of bronchiogenic carcinoma in the human male it was of special interest that among the tarred mice 25 of the cancers appeared in females and only 11 in males.

Successful transplantation of the experimentally produced cancers into normal mice was easily accomplished, and in one instance a transplantation has been carried out through more than 30 generations. Of course the importance of the successful transplantations is the positive evidence of malignancy of the growth which they demonstrate.

An observation of importance that we made in connection with the experiments was that the average time of appearance of a cancer was after 71 weeks of painting. This period of time represents a little more than one-half the average life-span of the mouse, which is ordinarily a little more than two years. This time corresponds roughly with the period of smoking required for the production of a bronchiogenic cancer in the human. For our statistical observations demonstrated that 30 to 50 years of smoking precede the appearance of a bronchiogenic carcinoma, a period roughly corresponding to one-half the life span.

*For details of the experimental work our original article (Wynder, Graham and Croninger, 1953) should be consulted.
Our experiments demonstrate beyond a possibility of doubt that cigarette smoke contains something which is carcinogenic for the skin of mice.

Is this finding of significance in relation to the question of human bronchiogenic carcinoma?

It would seem to the writer that, even when taken alone, the finding of a carcinogenic substance in cigarette smoke is of very great significance. When combined with the findings of the statistical studies the importance
of these experimental observations is greatly increased. To many the fact that all the published statistical studies point in the same direction together with now the successful production of epidermoid cancer in mice by painting the skin with the tar derived from cigarette smoke makes the chain of evidence incontrovertible. Others, however—and these are usually heavy cigarette smokers—decry the significance of our experimental results. They state that no absolute proof has been produced that there is any etiologic relationship between cigarette smoking and cancer of the lung.

It must be admitted that the proof of a definite relationship does not exist. To establish such proof to the satisfaction of the “die-hards” would require human experimentation carried out on the same individuals for more than a quarter of a century. Obviously such experiments cannot be conducted. Perhaps one could say that if the agent involved in the case were something less desired by the users of it than are cigarettes by their habitues there would be no difficulty in the general acceptance of the evidence. If, for example, the findings pointed to a substance like spinach as the guilty party instead of the habit-forming cigarette, would there be as much difficulty in accepting the evidence?

By many of the writers on this subject there is too much of a tendency to consider bronchiogenic carcinoma as if it were one disease. On the contrary there is much evidence to indicate that there are several varieties which are so different from each other that probably they represent actually different diseases. At least three varieties can be easily distinguished with different etiologies. The fact that smoking is not a causative factor in at least two of the three varieties leads to confusion in the minds of some observers who are not aware of the differences because, as they state, they can cite cases in which the patients never smoked.

The three varieties which seem to me to be clearly distinguishable from each other are:

1. The epidermoid or squamous cell. Sometimes the structure of this tumor is not clearly differentiated, and for that reason I like to include in this group the so-called “undifferentiated” cancers. This group is the common bronchiogenic carcinoma which in our experience constitutes well over 90 per cent of all bronchial cancers. At the present time it occurs much more commonly in the male. It is found very rarely in a non-smoker. It is this variety of lung cancer which has shown the very striking increase in incidence.

2. The adenocarcinoma. When typical this tumor has several characteristics which set it apart from the epidermoid cancer. For one thing, our statistical studies showed that it has a much less close relationship to smoking. In our series, out of 39 men with adenocarcinoma no fewer than four (10 per cent) were non-smokers, whereas among the other 605 men with bronchiogenic carcinoma the proportion of non-smokers was only 1.3 per cent. Even more remarkable was the fact that of 15 women with adenocarcinoma 13 were non-smokers. Another characteristic of the adenocarcinoma which distinguishes it from the epidermoid variety is that it occurs with about equal frequency in the two sexes. Again, the adenocarcinoma has a special tendency to involve younger people; or, to put it
in another way, whenever a young person has a bronchiogenic carcinoma it is nearly always an adenocarcinoma. Olson (1935) states of 576 cases of lung cancer compiled from the literature by Brunn in 1926, 12 per cent were in the age group 20-29, and all of them were adenocarcinoma. These characteristics seem to set off this tumor from the more common epidermoid cancer and to suggest that it is a different disease entity with a different etiology. Perhaps in at least some cases the adenocarcinoma has had

**Figure 6**: Advanced carcinoma (2 lesions) in another mouse at 590 rays of painting.—

**Figure 7**: Photomicrograph of lesion at left.

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its origin in a so-called bronchial adenoma which has become malignant. In 1938 Womack and I presented evidence that the so-called bronchial adenoma is a potentially malignant tumor capable of producing both regional and distant metastases. Such an idea at that time was not generally accepted but there are few who oppose it now. A common microscopic pattern seen when the tumor has become malignant is that of an adenocarcinoma. It would seem reasonable to conclude therefore that at least some of the adenocarcinomas have arisen in bronchial adenomas.

(3) The so-called alveolar-cell carcinoma. This type is rare compared with the other two types. Both the gross appearance of the involved lung and the microscopic characteristics of the tumor resemble very closely the disease of sheep known by the South African word, “jagziekte.” It is probably due to a virus.

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CONCLUSIONS

(1) A very remarkable increase in the incidence of bronchiogenic carcinoma has occurred in the last 25 years. From having been a curiosity in 1930, by 1950 it was so common that it had become the most frequent cancer in the male sex.

(2) No less than 12 statistical studies have shown a definite etiologic relationship between the disease and excessive cigarette smoking. Of equal importance, perhaps, is the fact that no careful study has been published which fails to show that relationship.

(3) The statistical evidence has been strongly supported by the experimental production of epidermoid carcinoma in the skin of CAF₁ mice by painting the skin with tar obtained from cigarette smoke. The incidence of cancer production was 44.4 per cent in 81 tarred mice.

(4) A mistake is commonly made in thinking that bronchiogenic carcinoma is a single disease. Actually there seem to be at least three separate varieties with different etiologies.

RESUMEN

1. En los últimos 25 años ha habido un notable aumento en la frecuencia del carcinoma bronquigénico. Siendo una curiosidad en 1930, ya en 1950 es tan común que se ha convertido en el cáncer más frecuente en el sexo masculino.

2. No menos de doce estudios estadísticos han demostrado de finidamente una relación etiológica entre la enfermedad y el fumar excesivo. De igual importancia quizás, es el hecho de que no se ha ya publicado un estudio cuidadoso que deje de mostrar esa relación.

3. La evidencia estadística es soportada fuertemente por la producción experimental del carcinoma epidermoide de la piel de los ratones CAF por medio de las embrocaciones de la piel con el alquitrán obtenido del humo de cigarrillos. La incidencia de la producción del cáncer fue de 44.4 por ciento en 81 ratones alquitranados.
4. Es un error común el considerar que el carcinoma bronquiogénico es una sola enfermedad. De hecho parece que hay cuando menos tres diversas variedades con etiologías diversas.

RESUME
1. Dans les 25 dernières années, on a noté une augmentation très importante de la fréquence du cancer bronchique. Considéré comme une curiosité en 1930 il était si répandu en 1950 qu'on pouvait le considérer comme le cancer le plus fréquent dans le sexe masculin.

2. Douze études statistiques au moins ont montré une relation étiologique incontestable entre cette affection et la consommation excessive de cigarettes. Peut-être faut-il attacher la même importance au fait qu'aucune étude attentive n'a été publiée concernant les cas où cette relation n'a pu être mise en évidence.

3. Les constatations statistiques ont été renforcées solide par la production de cancers épidermoides sur la peau de souris après application de goudron extrait de la fumée de cigarette. Sur 81 souris ainsi préparées, il y eut 44.4% de cancer.

4. C'est une erreur commune de penser que le cancer bronchique est une maladie simple. Actuellement, il semble qu'il y a au moins trois variétés différentes de cancer avec des étiologies diverses.

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