# The Role of Carcinogens, Especially Those in Cigarette Smoke, in the Production of Precancerous Lesions



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During the past 5 years we have been engaged in a study of the changes in the tracheobronchial tree brought about by inhaled irritants, especially those in cigarette smoke. The inhaled substances are widely distributed over the inner surface of the tracheobronchial tree.

When the bronchial epithelial surface is subjected repeatedly to a carcinogenic agent such as cigarette smoke a number of changes which may be regarded as precancerous as well as in situ cancer may occur at several different areas. Our studies have attempted to answer three propositions in connection with these changes.

1. If inhalants of one sort or another are a major factor in the causation of lung cancer, one might expect to find such changes in the remaining bronchial epithelium of persons who died of bronchogenic carcinoma.

2. One would then expect to find similar changes in the bronchial epithelium of persons who died of causes other than lung cancer, but who had been heavily exposed to potential carcinogenic inhalants.

3. In contradistinction, one ought to find an absence of these changes in a bronchial tree not exposed to these carcinogenic agents.

It is important to establish what the changes are in the epithelium of the tracheobronchial tree which lead up to the precancerous lesions. We have divided the findings into those in which the cilia are still present, namely, basal cell hyperplasia; and those in which cilia are absent, namely, stratification; squamous metaplasia; and car-

The author gratefully acknowledges the co-operation of the Medical Illustration Department of the Veterans Administration Hospital, East Orange, New Jersey.

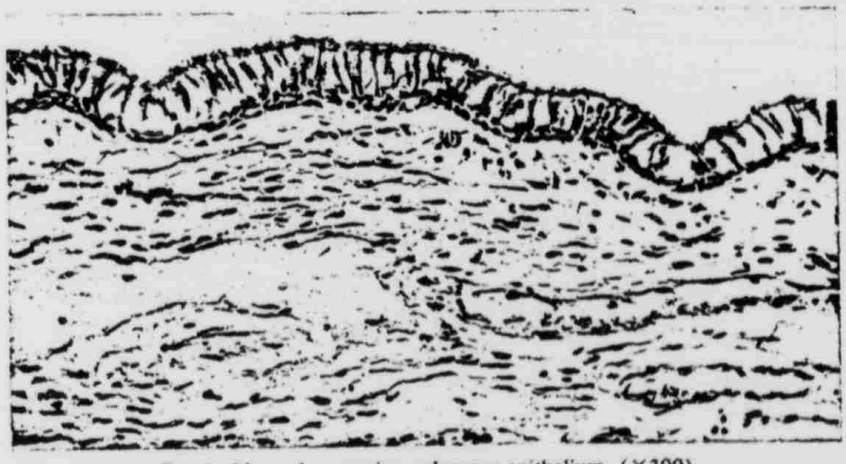


FIG. 1. Normal appearing columnar epithelium. (×300)



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cinoma in situ. It is our impression that inhaled carcinogens affect the basal cells and the subsequent changes result from an alteration and increase in the number of these cells. In order to clarify our interpretation of these terms which have been mentioned they will be described in detail.

## CHANGES WITH CILIA PRESENT (BASAL CELL HYPERPLASIA)

The basal cells lie along the *tunica propria*. They have scanty cytoplasm and have small, dark, oval or round nuclei (Fig. 1). Three or more rows of basal cells are classified as basal cell hyperplasia (Fig. 2). In extreme degrees, basal cell hyperplasia may be more than 20 rows in depth with the cilia intact. Normal basal cell hyperplasia is not a precancerous lesion. Lying among these normal basal cells there may be others which show varying degrees of alteration of the nuclei from slight to those which have the characteristics of neoplastic cells (Fig. 3). The number of these atypical cells and the degree of atypism we found parallels the amount of the inhaled carcinogens. Mitotic figures and giant nuclei increase as the degree of atypism advances.

## CHANGES WITH CILIA ABSENT; STRATIFICATION; SQUAMOUS METAPLASIA; CARCINOMA IN SITU

Proliferating basal cells may replace the overlying columnar cells and attached cilia. We have arbitrarily called this change "stratification" when there were no more than 4 rows of such cells and "squamous metaplasia" when there were 5 or more rows present (Fig. 4). In the last group, the epithelium is made up of larger cells and resembles squamous epithelium seen elsewhere in the body. Normal-appearing stratification and squamous metaplasia are not precancerous lesions. Atypical cells may be present

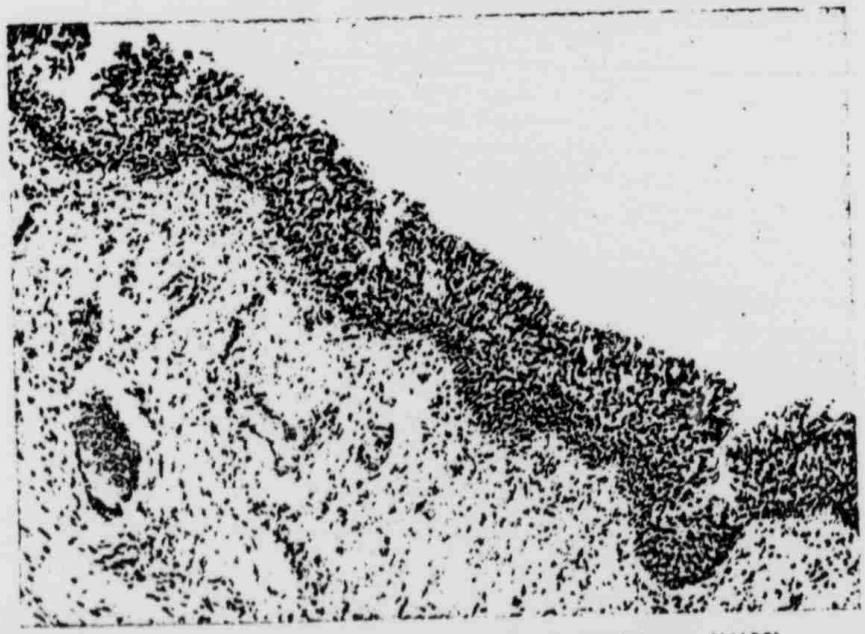


FIG. 2. Basal cell hyperplasia of a moderately advanced degree. (×125)


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among the normal cells. There may be only a few such cells and these vary but slightly from the normal cells. In the more advanced stages there is an increase in the number of these atypical cells as well as the degree of atypism with an increase in the number of mitoses and giant nuclei. In the most advanced degrees of atypism where more than 90 per cent of the cells are neoplastic in nature, there is generally a flattening of the cells on the superficial surface (Fig. 5). We consider the lesion to be carcinoma in situ when all the cells in it are atypical and the basement membrane is intact. In carcinoma in situ there is cellular disorganization, with loss of the usual layering; the nuclei show a great variation in size, shape and chromatin content, nu-



FIG. 3. Basal cell hyperplasia showing atypism to an advanced degree. (×550)

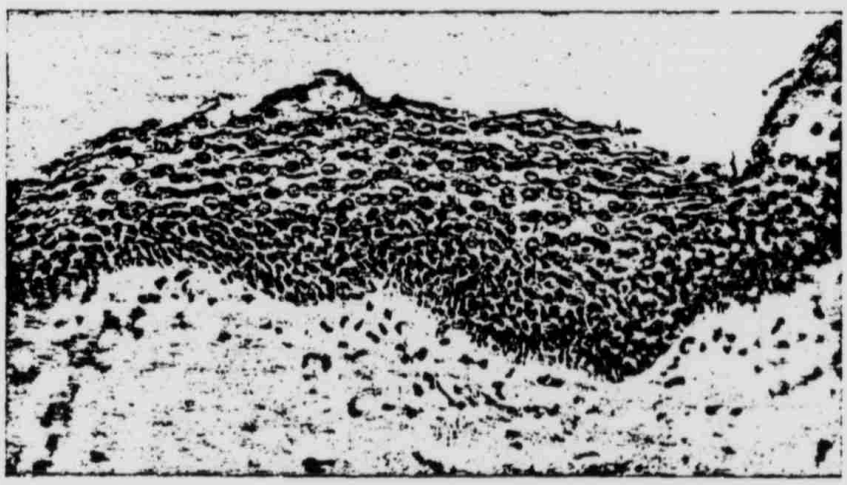


FIG. 4. Normal-appearing squamous metaplasia. (×475)


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clear hyperchromatism is frequent; there is an increased number of mitoses and they are often atypical; the nuclear cytoplasmic ratio is increased (Figs. 6 and 7).

During this 5-year period, 3 separate, but continuing studies have been carried out to test the 3 propositions previously mentioned. Individual cases were used in the



FIG. 5. Squamous metaplasia showing an advanced degree of atypism. There is a flattening of the cells on the superficial surface. (×575)



FIG. 6. Carcinoma in situ. Giant nuclei are present toward the superficial surface. (×575)


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first two studies. In the third study, fewer slides from each of the cases used were examined. This was based upon an analysis of earlier data that indicated that a sample of 55 sections from each subject was an adequate number to examine for the purpose at hand.

Based upon an analysis of the findings during this 5-year period in answer to the first proposition, the bronchial epithelium of individuals dying of lung cancer showed all stages of precancerous alteration up to frankly invasive carcinoma. The hypothesis of whether the inhalation of cigarette smoke was a carcinogenic agent capable of producing such changes was tested in individuals who died of causes other than lung cancer. In all three studies, the least number of findings was observed in those cases who either did not smoke or smoked only occasionally. The changes increased proportionately with the amount of cigarettes that the individual had smoked. We believe that this confirms the first and second propositions.

A high incidence of carcinoma in situ in nonsmokers in our second report led us to believe that we were including cases of squamous metaplasia in this category. We then set up strict criteria for the recognition of carcinoma in situ and atypical cells and the exclusion of all other lesions from that category. Thus, in our final study, we did not find a single instance of a carcinoma in situ in the nonsmokers or occasional smokers, and only 0.3 per cent of the slides in less than "half-a-pack" a day cigarette smokers showed these findings. Those who smoked "two packs" a day or more showed 11.4 per cent of the slides with carcinoma in situ and those who died of lung cancer had 15.0 per cent so involved. This confirms the third proposition (Fig. 8).

Therefore, it is our belief that the ex-

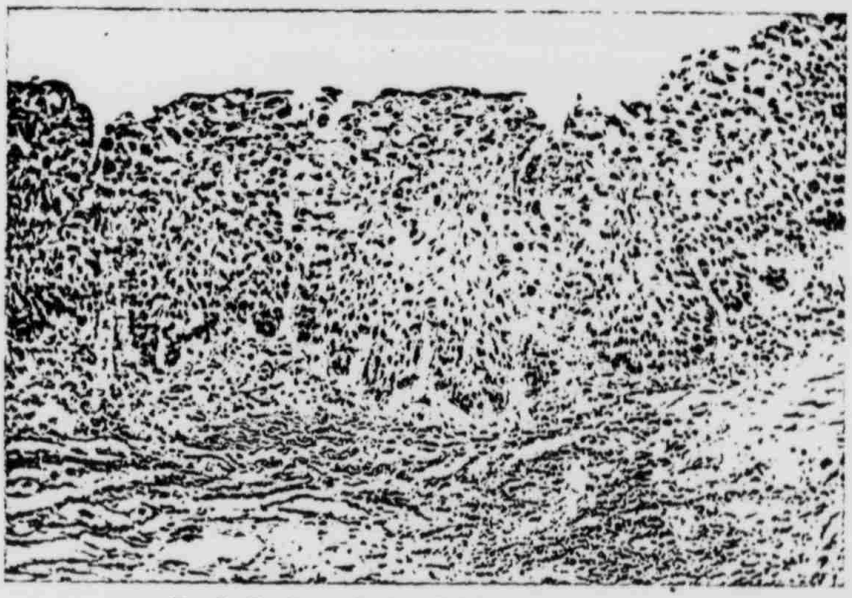


FIG. 7. Carcinoma in situ. Cellular atypism is present throughout the entire surface. (×150)


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tensive alterations of the epithelial lining in our cases of bronchogenic carcinoma lends credence to the belief that inhaled carcinogens play an important role in the development of lung cancer. That this is an almost universal occurrence is seen in the fact that there is a history of inhaled carcinogens in every case of bronchogenic carcinoma in this study. The single most important of these inhaled carcinogens is found in cigarette smoke. Among other inhaled carcinogens which are known to have produced lung cancer are chromates and uranium.

Although it is known that the air of urban communities may contain carcinogens, to our knowledge no one has proved that breathing such air alone can cause cancer of the lung. The fact that atypical epithelial changes can be found in the tracheobronchial tree of nonsmokers and occasional smokers points to the fact that inhaled air pollutants may play some role in the development of atypical epithelial changes. Bronchogenic carcinoma occurring in the absence of a verified history of smoking or of exposure to other known carcinogenic agents is extremely rare in men. We have never seen such a case.

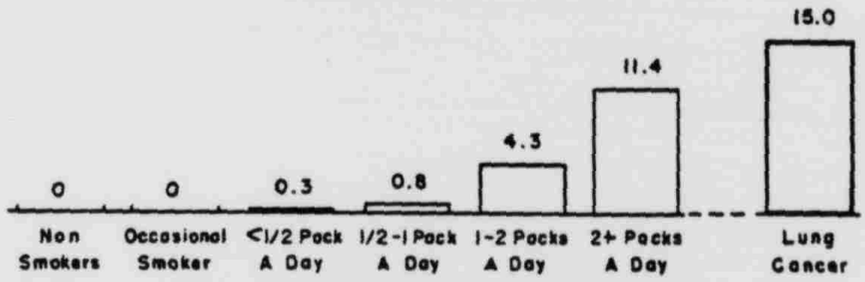



FIG. 8. Per cent of slides with carcinoma in situ.

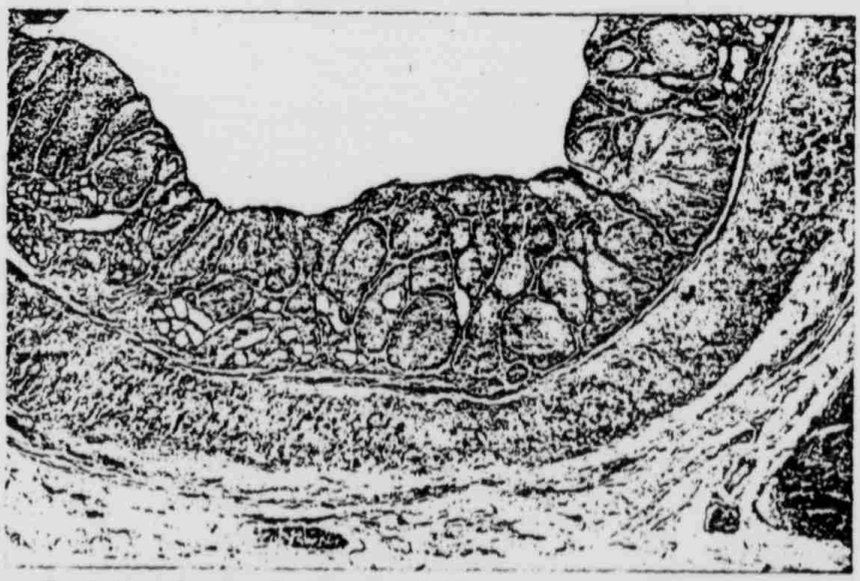


FIG. 9. Early invasion of carcinoma which in areas extends to the cartilage. (×4)


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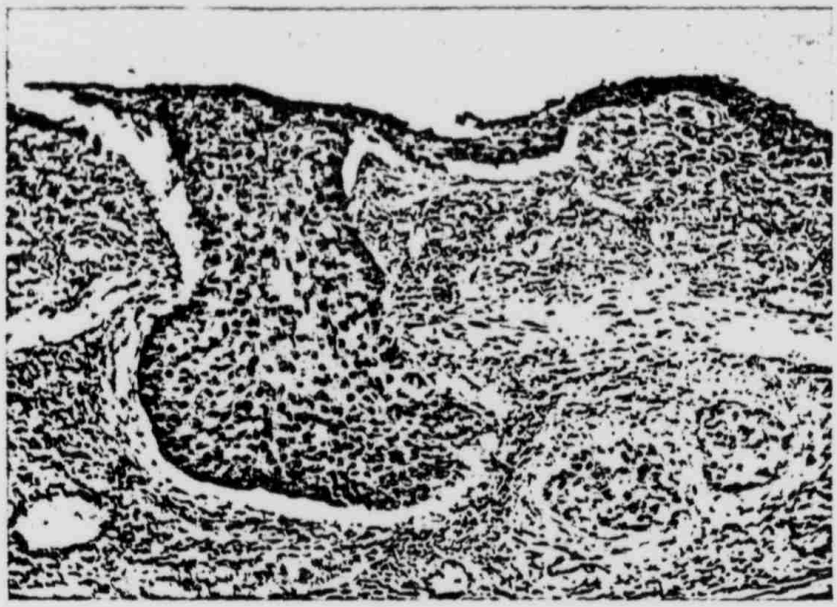


FIG. 10. Early invasion in an area adjoining carcinoma in situ. (×150)

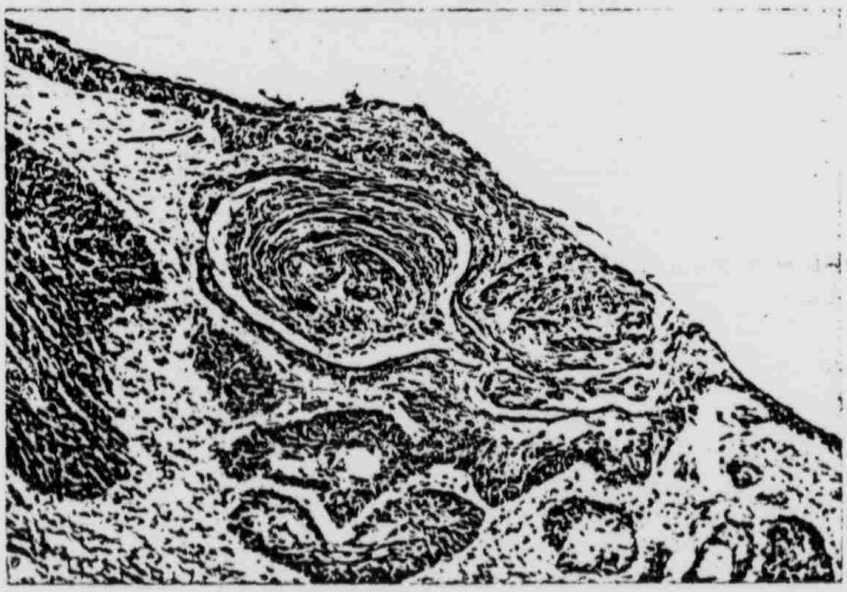


FIG. 11. Early invasion of carcinoma showing pearl formation at this site. (×150)


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The relationship of carcinoma in situ to early invasion has been discussed in a number of publications, particularly in relationship to cancer of the cervix. The high incidence of carcinoma in situ in cases dying of bronchogenic cancer suggests a close relationship also in the lung. In our final study, we observed 23 instances of early invasion and in every instance the invasion occurred at the site of a carcinoma in situ (Figs. 9 to 11).

We hope that our future study of former cigarette smokers who have discontinued the practice will shed some light on the reversibility of these precancerous lesions. Experimental studies indicate that some of these lesions may be reversible in rats. Whether or not such a reversal occurs in humans has not been proved.

## SUMMARY

A study of the changes in the tracheobronchial tree in cases dying of bronchogenic cancer shows all stages of epithelial alteration up to the development of invasive carcinoma. In individuals dying of causes other than lung cancer with verified smoking histories available, similar changes are present. The least number of such changes is present in nonsmokers with a progressive increase as the amount of smoking increases. No carcinoma in situ has been found in the non- or occasional cigarette smoker.

Cigarette smoking is the single most important cause of bronchogenic cancer in men today. In our studies, precancerous lesions have been always present in cases dying of lung cancer. Every one of these gave a history of having smoked. Similarly, precancerous lesions were always observed in the cases where there is a history of heavy cigarette smoking. Air pollutants other than cigarette smoke seemed to have played only a minor role in the production of such lesions in this study.

Early invasion when found occurring in 23 instances was always associated with a carcinoma in situ. The question of reversibility of carcinoma in situ in man awaits further study.

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DR. OCHSNER: The one person who has probably done more to show early diagnosis is our next speaker: Dr. Katharine R. Boucot, Professor of Preventive Medicine and Clinical Professor of Medicine, Woman's Medical College of Pennsylvania, Philadelphia, Pennsylvania. Dr. Boucot has done a tremendous amount of work on the subject and we are very happy to have her on the panel. She will speak on "The Early Detection of Bronchogenic Cancer." Dr. Boucot.


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