The New England
Journal of Medicine

Volume 256 JANUARY 17, 1957 Number 3

CHANGES IN THE BRONCHIAL EPITHELIUM IN RELATION TO SMOKING AND CANCER OF THE LUNG*

A Report of Progress

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MANY investigators have reported an association between the occurrence of lung cancer and exposure to certain dusts and vapors such as uranium and chromate dusts, general air pollution and cigarette smoke.[1-21] When inhaled, presumably, these substances are widely distributed over the inner surface of the tracheobronchial tree.

When a carcinogenic agent is applied to the tissue, a number of changes such as hyperplasia and metaplasia usually precede the appearance of cancer, and neoplastic changes are apt to occur at several different points. Therefore, if inhalants of one sort or another are a major factor in the causation of lung cancer, one might expect to find hyperplasia, metaplasia and early neoplastic changes in the remaining bronchial epithelium of persons who died of bronchogenic carcinoma. Furthermore, one would expect to find similar changes, but to a less marked degree, in the bronchial epithelium of persons who died of some other cause, but who had been heavily exposed to potential carcinogenic inhalants.

The present study was undertaken to test these two hypotheses. Since it has not yet been completed, the findings and conclusions reported here should be regarded as a progress report subject to later modification.

A previous report from this institution described a method of studying the histologic changes in the tracheobronchial tree.[22] At that time the difficulties of preserving the epithelium were pointed out.

The preliminary study showed three important changes in the bronchial epithelium — namely, basal-cell hyperplasia, stratification and squamous metaplasia. In each slide studied, the presence or absence of these changes was recorded. When the findings were tabulated it was observed that there was a definite difference in the amount and extent of these changes in the tracheobronchial trees of nonsmokers as compared with moderate and heavy smokers. The same contrast held when the nonsmokers were compared with the patients with carcinoma of the lung, all of whom were smokers.

After the preliminary report we were assisted by Dr. E. Cuyler Hammond, of the American Cancer Society, in working out a system for obtaining smoking histories and a means of tabulating the histologic changes.

MATERIAL

One hundred and fifty patients who died and were autopsied at the Veterans Administration Hospital, East Orange, New Jersey, were studied. All were white men whose ages ranged from twenty-two to eighty-eight, but over two thirds were between the ages of fifty and seventy years. Most of the patients lived in urban industrial areas of New Jersey. No single occupation predominated in the series, and among them were salesman, bus driver, clerk, real-estate agent, painter and so forth. The histories of smoking habits, occupations and places of residence were obtained from the family by a trained social worker. Whenever possible an interview was obtained from the patient himself upon entrance to the

*From the Laboratory Service, Veterans Administration Hospital, East Orange, New Jersey.
Presented in part at the third National Cancer Conference, Detroit, Michigan, June 4-6, 1956.
Supported by a research grant from the American Cancer Society.

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hospital. The material was studied only after the smoking histories had been obtained. All patients dying of lung cancer were included. Those dying

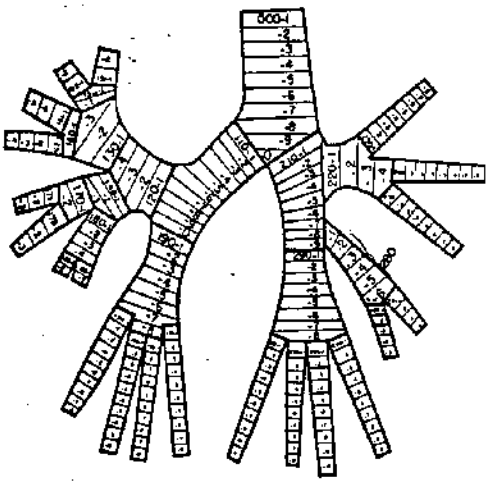

FIGURE 1. *Schematic Diagram of the Tracheobronchial Tree, Showing the Distribution of the 208 Sections.*

of other causes were included only if an adequate smoking history could be obtained. To have as large a number of cases as possible in groups suitable for comparison, minor categories such as cigar and pipe

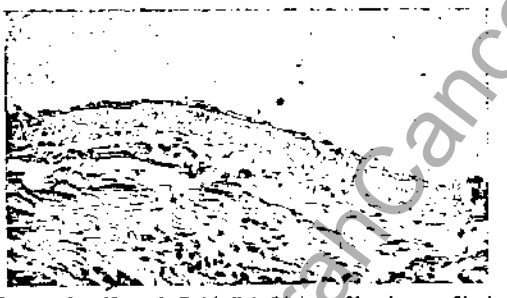

FIGURE 2. *Normal Epithelial Lining, Showing a Single Layer of Basal Cells (X150).*
Ciliated columnar cells lie above these.

smokers and former cigarette smokers were temporarily excluded from the study.

METHODS

As soon as possible after death the tracheobronchial tree was dissected out of the lungs by a method previously described. The difficulty with denudation was largely overcome in the latter part of the study by early fixation of the lungs with formalin and prompt dissection of the lungs from the tracheobronchial tree. The specimen was thus separated from contiguous structures and isolated in clean, fresh formalin within twenty-four hours of the removal of the lungs. It was then divided into 208 portions, as shown in Figure 1. In cases of lung cancer some portions of the tracheobronchial tree had been destroyed by the disease and were not available for study. All the available portions were imbedded in paraffin, and one slide was prepared from each block.

A total of 28,638 slides, each with a punch-card counterpart, were made in this way in the 150 cases studied to date. Each slide was examined by at least two pathologists, and a large number were examined three, four and five times. In all, about 80,000 examinations were made.

To avoid bias on the part of the microscopists, they were kept ignorant of the smoking histories and the clinicopathological data. Since not all the slides prepared had sections showing epithelium it was decided to include in the study only cases that had a minimum of 100 slides with any epithelium present. Of these, at least 70 slides had to have 50 per cent of the epithelium available. Thus, 29 cases failed to

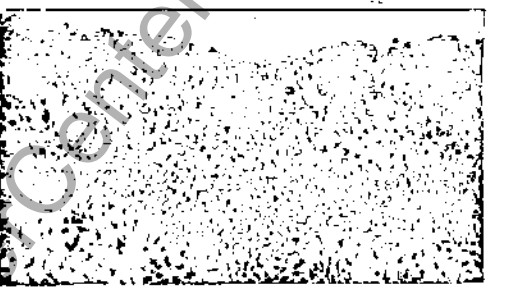

FIGURE 3. *Basal-Cell Hyperplasia (X150).*
There is a moderate increase of normal basal cells. Above these are ciliated columnar cells.

meet these minimum requirements and were eliminated. It was not feasible to apply this rule to the cases of lung cancer. An additional 4 cases were

FIGURE 4. *Stratification (X160).*
There is a flattening of the epithelial cells on the surface. Cilia are absent.

eliminated because of mixed smoking histories since this group was too small for analysis. The results in this paper are based on the analysis of the remaining 117 cases.

Findings

A number of changes were observed in the tracheobronchial epithelium.

Basal-Cell Hyperplasia

The basal cells lie along the tunica propria. They have scanty cytoplasm and small, dark, oval or round nuclei (Fig. 2). Since there has been some disagreement among histologists regarding what constitutes the normal number of basal cells, only three or more rows of typical basal cells have been classified as basal-cell hyperplasia (Fig. 3).

Figure 5. *Squamous Metaplasia (X160).*
A thick layer of epithelial cells resembles squamous epithelium in other sites.

Stratification

The bronchial surface mucosa in cases of stratification shows an absence of the ciliated cells and some flattening of the epithelial cells toward the lumen.

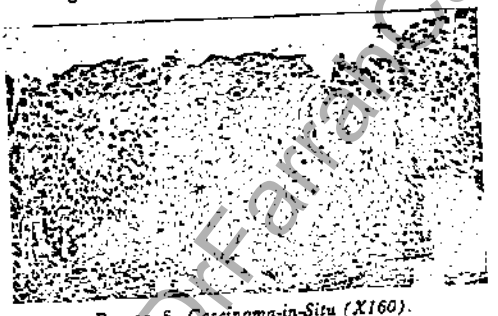

Figure 6. *Carcinoma-in-Situ (X160).*
The thickened epithelium shows a disorientation and loss of layering of the cells, with an intact basement membrane. There is a great variation in the size and shape of the nuclei.

The process never involves all the deeper layers (Fig. 4).

Squamous Metaplasia

In this group the epithelial lining is generally thicker and is made up of larger cells. It resembles squamous epithelium seen elsewhere in the body and involves the full thickness of the surface mucosa (Fig. 5).

Carcinoma-in-Situ

We have applied the same criteria here as are accepted for intraepithelial carcinoma in other sites[33-35] in the body and as those applied by Black and Ackerman[36] in their study of bronchogenic carcinoma (Fig. 6). These are as follows: the basement membrane is intact; there is cellular disorganization, with loss of the usual layering; the nuclei show a great variation in size, shape and chromatin content (nuclear hyperchromatism is frequent); there is an increased number of mitoses, and they are often atypical; the nuclear-cytoplasmic ratio is increased; and the epithelium is often, but not always, thickened, a finding similar to that observed in the larynx by Stout[38] and by Altmann, Ginsberg and Stout.[39]

Two types of intraepithelial neoplastic alterations were observed. One group, the definite carcinoma-in-situ, met the criteria set forth above. The second group, the questionable carcinoma-in-situ, although borderline, could not be certainly classified as definite carcinoma-in-situ because one or two of the criteria listed above were absent.

Table 1: *Distribution of Patients with Three or More Rows of Basal-Cell Hyperplasia.*

Percentage of Slides with Three Rows	Deaths Not Due to Lung Cancer			Deaths Due to Lung Cancer
	Patients who never smoked regularly	Patients who smoked <1 package daily	Patients who smoked 1 package or more daily	
<5	3	4	—	—
5- 9	3	3	2	1
10-14	4	2	6	—
15-19	1	3	6	5
20-24	1	2	3	3
25-29	1	1	5	1
30-34	—	1	8	3
35-39	—	1	2	4
40-44	1	—	3	1
45-49	—	—	1	3
50-54	1	—	1	2
55-59	1	2	1	4
60-64	—	—	2	—
65-69	—	—	2	2
70-74	—	1	—	3
75-79	—	—	—	—
80-84	—	—	4	1
85-89	—	—	—	1
90-94	—	—	1	—
95-100	—	—	—	—
Totals	16	20	47	34
Mean percentages	18.6	22.0	36.1	43.5

Results

To test the two hypotheses the cases were divided into two groups. In one, manifest carcinoma

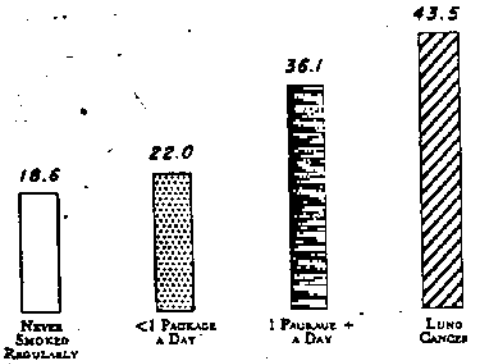

FIGURE 7. *Percentage of Slides with Basal-Cell Hyperplasia Involving Three or More Cell Rows.*

of the bronchus was found by ordinary autopsy procedure. The other group was evaluated according to the smoking history.

Lung Cancer

Thirty-four patients died of bronchogenic carcinoma. Their average age was fifty-eight. Nineteen

TABLE 2. *Distribution of Patients with Five or More Rows of Basal-Cell Hyperplasia.*

Percentage of Slides with 5 Rows	Deaths Not Due to Lung Cancer			Deaths Due to Lung Cancer
	Patients who never smoked regularly	Patients who smoked <1 package daily	Patients who smoked 1 package or more daily	
0	4	4	1	—
<5	9	8	18	5
5- 9	1	5	10	11
10-14	2	—	8	8
15-19	—	2	1	5
20-24	—	1	3	1
25-29	—	—	3	—
30-34	—	—	2	1
35-39	—	—	—	2
40-44	—	—	1	1
45-49	—	—	—	2
50-54	—	—	—	—
55-59	—	—	—	—
60+	—	—	—	—
Totals	16	20	47	34
Mean percentages	2.9	5.6	10.8	15.0

of them smoked one package or more of cigarettes a day; 10 smoked cigarettes regularly, but less than a package a day, 4 were former regular cigarette smokers and 1 smoked a pipe and cigars, but not cigarettes.

A total of 5780 slides were obtained from the 34 cases, but 880 were completely denuded of epithelium. There were 4900 with epithelium, or an average of 144 usable slides per case. The findings are expressed in percentages of useful slides in each case with specified findings.

Basal-cell hyperplasia. The cases of lung cancer averaged 43.5 per cent of the slides with basal-cell hyperplasia — that is, having three or more rows, the range being from 9.0 per cent to 85.0 per cent (Table

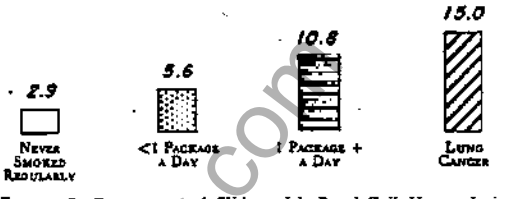

FIGURE 8. *Percentage of Slides with Basal-Cell Hyperplasia Involving Five or More Cell Rows.*

1 and Fig. 7). The findings were present in both lungs and in the trachea. The depth of hyperplasia varied considerably. Therefore, a quantitative estimate was made by a count of the average number of rows of basal cells in each case. For cases of lung cancer the slides showed basal-cell hyperplasia with

TABLE 3. *Distribution of Cases with Stratification.*

Percentage of Slides with Stratification	Deaths Not Due to Lung Cancer			Deaths Due to Lung Cancer
	Patients who never smoked regularly	Patients who smoked <1 package daily	Patients who smoked 1 package or more daily	
0	6	6	5	2
<5	3	7	17	11
5- 9	5	2	6	3
10-14	2	1	6	8
15-19	—	2	5	1
20-24	—	1	3	2
25-29	—	—	1	3
30-34	—	—	1	1
35-39	—	—	1	1
40-44	—	1	2	—
45-49	—	—	—	1
50-54	—	—	—	—
55-59	—	—	—	1
60+	—	—	—	—
Totals	16	20	47	34
Mean percentages	4.2	7.1	10.4	13.4

an average depth of three cell rows in 5.3 per cent and one of four cell rows in 23.2 per cent. Basal-cell

hyperplasia of five or more rows was present in 15.0 per cent of the slides, and the changes were found in more than 25 per cent of the slides in 25 of the 34 cases in this group (Table 2 and Fig. 8).

Stratification. This change was apparent in 13.4 per cent of the slides of the patients with lung cancer (Table 3 and Fig. 9). In fact, of the 34 patients involved, all but 2 had some slides showing stratification. In 1 extreme case stratification was found in 57.0 per cent of the slides.

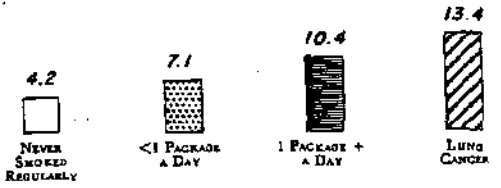

FIGURE 9. *Percentage of Slides with Stratification.*

Squamous metaplasia. This finding was present in 11.7 per cent of the slides of the patients with lung cancer, and some degree of metaplasia was found in 31 of the 34 cases in this group. In 1 extreme case squamous metaplasia was seen in 48 per cent of the slides (Table 4 and Fig. 10).

TABLE 4. *Distribution of Patients with Squamous Metaplasia.*

Percentage of Slides with Squamous Metaplasia	Deaths Not Due to Lung Cancer			Deaths Due to Lung Cancer
	Patients who never smoked regularly	Patients who smoked < 1 package daily	Patients who smoked 1 package or more daily	
0	5	1	5	3
<5	9	13	20	9
5- 9	2	5	6	10
10-14	—	—	1	5
15-19	—	1	4	1
20-24	—	—	3	1
25-29	—	1	1	2
30-34	—	—	2	3
35-39	—	1	3	—
40-44	—	—	—	1
45-49	—	—	—	1
50-54	—	—	—	—
55-59	—	—	—	—
60+	—	—	—	—
Totals	16	20	47	34
Mean percentages	1.9	6.3	9.5	11.7

Carcinoma-in-situ. Definite carcinoma-in-situ was found in 6.3 per cent of the slides of the patients with lung cancer (Table 5). Borderline carcinoma-in-situ was observed in another 6.7 per cent of the slides, making a total of 13.0 per cent involved by either definite or borderline carcinoma-in-situ.

These changes were observed in 28 out of 34 cases of carcinoma of the lung. In 1 case 49 individual slides showing definite carcinoma-in-situ were found, widely distributed in both lungs. This comprised 29.0 per cent of the usable slides in this case.

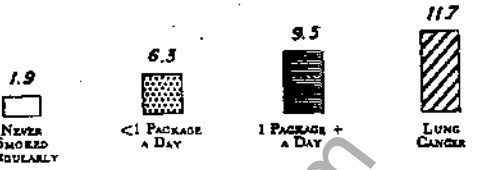

FIGURE 10. *Percentage of Slides with Squamous Metaplasia.*

Findings in Relation to Smoking

These 83 patients who had died without evidence of lung cancer by ordinary autopsy procedure were evaluated according to the same histologic criteria and were divided into three groups according to their smoking histories.

TABLE 5. *Distribution of Patients with Carcinoma-in-Situ, including Borderline Lesions.*

Percentage of Slides with Carcinoma-in-Situ, Including Borderline Lesions	Deaths Not Due to Lung Cancer			Deaths Due to Lung Cancer
	Patients who never smoked regularly	Patients who smoked < 1 package daily	Patients who smoked 1 package or more daily	
0	8	8	9	6
<5	5	6	17	7
5- 9	3	5	5	8
10-14	—	1	4	2
15-19	—	—	4	4
20-24	—	—	3	1
25-29	—	—	3	1
30-34	—	—	2	—
35-39	—	2	—	2
40-44	—	—	—	1
45-49	—	—	—	2
50-54	—	—	—	—
55-59	—	—	—	—
60+	—	—	—	—
Totals	16	20	47	34
Mean percentages	1.9	5.7	8.5	13.0

Group 1 — patients who never smoked regularly. There were 16 patients who had never smoked regularly.

Group 2 — patients who smoked less than one package of cigarettes a day. In this group there were

20 men who smoked regularly but less than one package a day.

Group 3 — patients who smoked one package or more a day. The largest number of cases (47) fell into this category.

The smoking histories in Groups 2 and 3 ranged from four to sixty years.

Basal-cell hyperplasia. In those who never smoked regularly, 18.6 per cent of the slides examined showed this finding, as compared with 36.1 per cent in the group smoking over a package a day. This difference is statistically significant ($P<0.01$). The average was 22 per cent in the patients smoking less than one package a day. Thus, there was a consistent trend in the amount of basal-cell hyperplasia with increased amount of smoking (Table 1).

TABLE 6. *Distribution of Patients with Definite Carcinoma-in-Situ.*

Percentage of Slides with Definite Carcinoma-in-Situ	Deaths Not Due to Lung Cancer			Deaths Due to Lung Cancer
	Patients who never smoked regularly	Patients who smoked <1 package daily	Patients who smoked 1 package or more daily	
0	11	8	12	8
<5	3	8	18	15
5- 9	2	1	4	5
10-14	—	1	5	2
15-19	—	—	6	—
20-24	—	2	1	—
25-29	—	—	1	4
30-34	—	—	—	—
35-39	—	—	—	—
40-44	—	—	—	—
45-49	—	—	—	—
50-54	—	—	—	—
55-59	—	—	—	—
60 + —	—	—	—	—
Totals	16	20	47	34
Mean percentages	1.0	4.1	6.0	6.3

Of interest is the fact that in the group who never smoked regularly, only 2.9 per cent of the slides showed five or more rows of basal-cell hyperplasia, whereas in those who smoked more than one package a day 10.8 per cent of the slides were so involved (Table 2). This difference is statistically significant ($P<0.01$). The group smoking less than one package a day showed 5.6 per cent of this degree of change.

Stratification. Of the patients who never smoked regularly 4.2 per cent of the slides had this alteration, as compared with 10.4 per cent in the group smoking over a package a day. This difference is statistically significant ($P<0.02$). Those who smoked less than one package a day showed 7.1 per cent of the slides involved with this change (Table 3).

Squamous metaplasia. Squamous metaplasia was found in 1.9 per cent of the slides of patients who had never smoked regularly, as compared with 9.5 per cent of those in the group smoking over a package a day. This difference is statistically significant ($P<0.01$). The average was 6.3 per cent in the patients smoking less than one package a day. There was a consistent trend in the amount of squamous metaplasia with increased amount of smoking (Table 4).

Carcinoma-in-situ. Definite carcinoma-in-situ was found in 1.0 per cent of the patients who had never smoked regularly, as compared with 6.0 per cent of those who smoked more than a package a day (Table 6 and Fig. 11). This difference is statistically significant ($P<0.01$). The average was 4.1 per cent in the patients who smoked less than one package a day.

Definite and borderline changes of carcinoma-in-situ were found in 1.9 per cent, 8.5 per cent and 5.7 per cent of the slides of the three respective groups.

Discussion

Before the histologic data presented can be directly related to smoking habits, several important factors must be considered.

Age

The question arises whether the changes are related to age since bronchogenic carcinoma is observed with greatest frequency in men fifty to seventy years old. In this study, holding smoking histories constant, there seemed to be a slight age trend. This could not be adequately tested because of the small number of cases in the series.

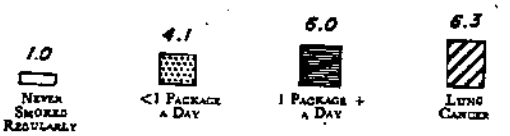

FIGURE 11. *Percentage of Slides with Definite Carcinoma-in-Situ.*

Occupation

Several unrelated industries have been associated with lung cancer such as mining ores in Schneeberg, chromate production, nickel refining, asbestos manufacturing and gas work. The mortality in chromate workers is fourteen times greater than would be normally anticipated. Gas-company employment, working in foundries and metal grinding are occupations that are also associated with an increased rate of bronchogenic carcinoma.

None of the patients in our series had worked in the occupations that are related to the increase in carcinoma of the bronchus.

Air Pollution

It is well established that carcinoma of the lung is more frequent in urban than in rural areas. This may be due in part to medical practices, but air pollution is undoubtedly involved. All the findings point to the fact that in the group of patients who had never smoked regularly there are changes in the tracheobronchial tree entirely similar in distribution but less extensive than those in the other three smoking categories or cancer of the lung. This suggests that inhalants present in the atmosphere may play a part in the etiology of cancer of the lung.

Inflammation

In inflammatory processes with ulceration, regeneration may result either in complete restoration of normal-appearing mucous membrane, stratification or squamous metaplasia. Although this process may have accounted for some of the changes recorded in this series, the absence of other residua of inflammatory diseases in the walls of the bronchi leaves no doubt that inflammation played only a small part in the production of the changes under discussion.

Constitutional Factors

One would certainly agree with Weller[39] that an unknown host factor, combined with irritation of the bronchial mucosa, is involved in the development of lung carcinoma. The hereditary aspect of the problem was not investigated in this study.

Relation of Data to Problem of Lung Cancer

The data presented may now be related to the hypotheses set forth at the onset. Are inhalants of one sort or another a major factor in the causation of lung cancer? If so, might one expect to find hyperplasia, metaplasia and early neoplastic changes in the remaining bronchial epithelium of persons who died with bronchogenic carcinoma? Furthermore, is it reasonable to expect similar changes in the bronchial epithelium of persons who died of some other cause but who had been similarly exposed to potential carcinogenic inhalants?

First to be considered are the findings in subjects who died of bronchogenic carcinoma. Specifically, in such cases basal-cell hyperplasia, stratification, squamous metaplasia and carcinoma-in-situ were diffusely distributed throughout the epithelium of the bronchial tree in both lungs as well as in the trachea. This is exactly what one might expect to find if the fatal cancer had been caused by some carcinogenic agent applied to the epithelium of the entire tracheobronchial tree. Thus, it is consistent with the theory that the inhalation of carcinogenic substances in dust, vapor or smoke is a major factor in the causation of lung cancer.

We have stated that no single occupation or group of occupations was represented with sufficient frequency for analysis. It is probable that all these men had been exposed in some degree to air pollutants associated with urbanization. Therefore, it is conceivable that the few changes noted in the lungs of some of the nonsmokers as well as some of the changes present in the lungs of smokers were due in part at least to inhalants other than tobacco smoked.

Next under consideration are the findings in subjects who died of causes other than lung cancer. Basal-cell hyperplasia, stratification, squamous metaplasia and definite carcinoma-in-situ were almost as common in the subjects who smoked one package or more a day as in those who died with carcinoma of the lung. These changes were less frequent in moderate cigarette smokers and still less frequent in men who had never smoked regularly. It should be noted that only 16 nonsmokers have thus far been studied, and this series will be expanded before the work is completed. We also hope to get an additional series of people who have never smoked and have never been exposed to air pollutants associated with urbanization.

Of great interest is the large number of definite carcinomas-in-situ discovered in this study. It must be noted that in the group that never smoked regularly only 5 out of 16 patients showed a few slides with this epithelial alteration. In contrast, 12 of 20 subjects smoking less than one package a day showed definite carcinoma-in-situ, and 35 of 47 of those smoking more than one package a day showed this change. This is comparable to the patients with lung cancer, 26 out of 34 of whom had carcinoma-in-situ. The mean percentage of carcinoma-in-situ was six times as much in the heavy smokers as it was in the nonsmokers and of a comparable range in the heavy smokers and the patients with carcinoma of the lung.

Summary and Conclusions

The histologic observations were recorded on 117 cases in which the tracheobronchial tree was divided into 208 sections except for those lost for pathologic reasons.

The cases were divided into two groups: those who died of bronchogenic carcinoma (34 patients), all of whom were smokers; and those who died of causes other than bronchogenic carcinoma. The findings in the latter group were tabulated according to their smoking histories, which were divided into three categories — namely, those who never smoked regularly or at all (16 patients), those who smoked under one package a day (20 patients) and those who smoked more than one package a day (47 patients).

Four changes in the epithelium were evaluated:

basal-cell hyperplasia; stratification; squamous metaplasia; and carcinoma-in-situ.

This histologic study shows that among people who died of causes other than lung cancer, basal-cell hyperplasia, stratification, squamous metaplasia and carcinoma-in-situ were least frequent in the group that never smoked regularly, with a progressive increase in the moderate and heavy smokers. The same but more extensive changes were observed in those who died of carcinoma of the lung.

Although definite carcinoma-in-situ was present in all groups, with a parallel rise in proportion to increasing cigarette consumption, there was an almost similar distribution of this change in those who smoked more than one package a day (6.0 per cent) and in the cases of bronchogenic carcinoma (6.3 per cent).

These findings are fully consistent with the hypothesis that inhalants of one sort or another are important factors in the causation of bronchogenic carcinoma.

The findings are also fully consistent with the theory that cigarette smoking is an important factor in the causation of bronchogenic carcinoma.

We are indebted to Dr. E. Cuyler Hammond and Mr. Lawrence Garfinkel for assistance in this study and to the Medical Illustration Department of the Veterans Administration Hospital, East Orange, New Jersey, for co-operation.

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INFECTIONS COMPLICATING CORTISONE THERAPY

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ANCON, CANAL ZONE

ONE of the most serious complications of cortisone therapy is infection. In the six years in which cortisone has been available for general use, this danger has been the subject of numerous clinical and experimental reports. However, much of the enthusiastic literature has not given this aspect sufficient emphasis. The purpose of this report is to present 6 cases seen in a period of one year in which infections developed during cortisone therapy. Four of these infections were due to bacteria, 1 to monilia, and 1 to histoplasmosis.

The corticosteroids are used in a wide variety of diseases, but their basic mechanism is still incompletely understood. However, there is no clinical or experimental evidence that they ever influence the etiologic agent to effect a cure. Rather, cortisone modifies the response of the host to the disease, and this may be of advantage in certain situations.

It would be expected that modification of the

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