The Role of Smoking in the Development of Lung Cancer



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During the past 10 years we have been engaged in studies of microscopic changes in the bronchial lining in relation to smoking and the development of lung cancer. The studies were undertaken to verify the epidemiologic findings of an increase in the lung cancer death rate in cigarette smokers as compared with the death rate of persons who had never smoked. Since the lung cancer death rate increases in ratio to the amount of cigarettes smoked per day, there should be extensive cellular changes in the lungs of persons who were heavy smokers but who died of causes other than lung cancer. The number of cigarettes consumed per day by persons having died of causes other than lung cancer should determine the number and the degree of changes in their lungs. There should be extensive changes also in the bronchial tubes of persons who died of lung cancer.

Three separate studies were made to answer two questions: (1) In individuals who died of lung cancer (squamous and undifferentiated), are there changes in the remaining bronchial epithelium that may be considered as preliminary stages in the development of lung cancer? (2) In individuals who died of causes other than lung cancer, are these changes present and are they proportional to the amount of cigarettes smoked? These questions have been answered fully in microscopic studies of the tracheobronchial trees of 339 men who died from causes other than lung cancer, and 63 from lung cancer. Up to 55 cross-sections of the bronchial tubes were studied in each case. The 339 non-lung cancer cases included 65 men who had never smoked cigarettes and 274 men who had smoked cigarettes in various amounts. More abnormal cellular changes and precancerous changes were found in the cigarette smokers. Not one section with an area of precancerous change was found in 65 nonsmokers. Furthermore, the number and the degree of these changes increased according to the daily number of cigarettes smoked. The lung cancer cases showed the most extensive changes.

Throughout our studies, a great deal of care was taken to keep the pathologic recordings as objective as possible. Serial numbers were assigned to the slides by the statisticians, who then put them in random order to prohibit the pathologists from studying all sections from one case at the same time. Thus, each slide had to be interpreted individually.

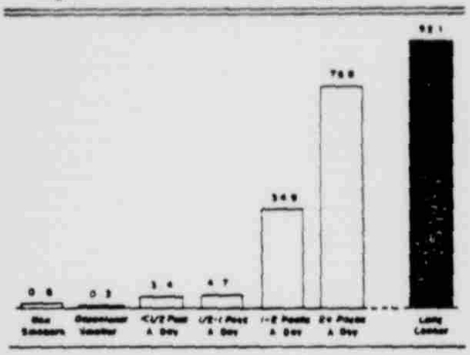
The pathologic findings were recorded on code sheets, and later punched on IBM cards for the purpose of analysis.

We have been particularly impressed with the distribution of cells with irregularly shaped anaplastic nuclei, which we have called *atypical* nuclei, in the bronchial lining (Table 1). These cells, which are structurally indistinguishable from cancer cells in invasive cancer, rarely were found in persons who had never smoked cigarettes (Figs. 1 and 2). The studies have shown that the number of such cells increases quite rapidly in persons who had smoked cigarettes, and the greater the quantity of cigarettes used each day, the greater the quantity

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TABLE 1. Per Cent of Slides With Lesions Showing 60 Per Cent or More Atypical Cells.



of such cells. Lesions with 70 per cent or more atypical cells were found seldom except in very heavy smokers and men who died of lung cancer.

LESIONS COMPOSED ENTIRELY OF ATYPICAL CELLS

Altogether, 956 out of 19,797 sections in the 402 cases studied had one or more lesions composed entirely of atypical cells. We have interpreted these as precancerous lesions (Figs. 3, 4, 5). Early primary invasive carcinoma of microscopic size were found in 23 of these 956 sections (Figs. 6 and 7). Of these 23 tiny primary carcinomas, 20 were found in the bronchial epithelium of 7 men who died of lung cancer. Two were found in a 60-year-old man who smoked 1 to 2 packages of cigarettes a day and died of rheumatic heart disease. One was found in a 58-year-old man who smoked 1 to 2 packages of cigarettes a day and died of carcinoma of the esophagus.



FIG. 2. Lesion with cilia present and with hyperplasia of the basal cells, showing a disorderly arrangement and advanced atypism of the nuclei. The atypical cells are approaching the surface (×470).



FIG. 1. Basal-cell hyperplasia with atypical nuclei. There is a disorderly arrangement of the cells (×600).



FIG. 3. An area of basal-cell hyperplasia with atypical nuclei merging with an area composed entirely of atypical cells (×150).

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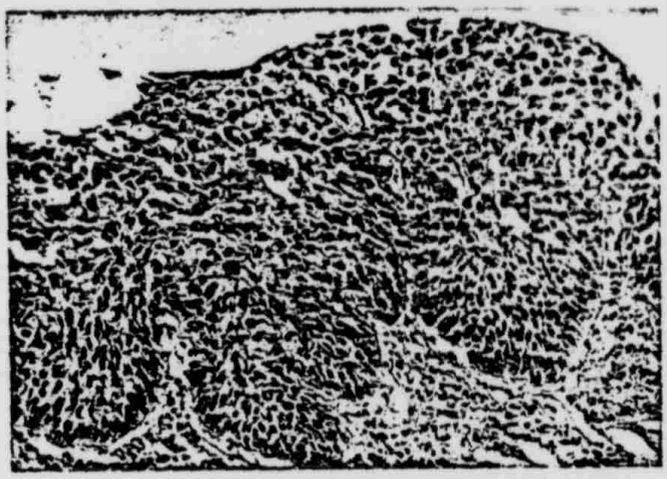


FIG. 4. An area, with cilia absent, composed entirely of atypical cells, resulting in a great thickening of the epithelium (the basement membrane is still intact (×120).

In each of the 23 sections with small primary carcinomas, other portions of the sections had areas composed entirely of atypical cells but with no indication of invasion. These areas merged into the area of definite invasive carcinoma. In addition, separate but similar areas composed entirely of atypical cells were found in some of these 23 sections. The cell structure and arrangement in these noninvasive areas was indistinguishable from that of the definite invasive carcinoma. Furthermore, in cases in which the subjects had died of lung cancer, the cells in these noninvasive areas were similar in appearance to those in the main large tumor mass. In the light of this, it seems reasonable to apply the term *precancerous* change to the noninvasive areas in these 23 sections as described above. This suggestion is based on

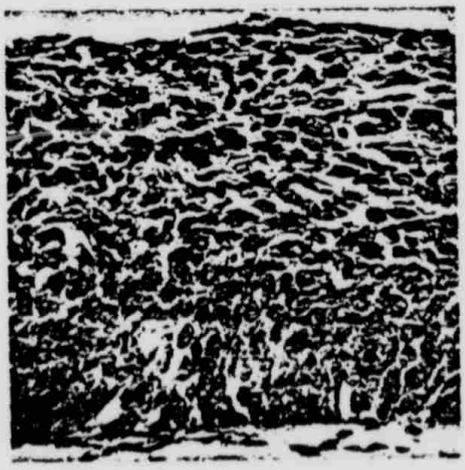


FIG. 5. Lesion, with cilia absent, composed entirely of atypical cells. The atypical cells are indistinguishable from invasive cancer present at another site in this case. The epithelium is thickened greatly, and the basement membrane is intact (×200).



FIG. 6. Lesion showing early invasion adjoining a zone of epithelium, with atypism of all the cells at the site (×165).

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FIG. 7. Lesion showing early invasive carcinoma extending to the cartilage at this site (×75).

the impression that, before invasion occurred, the definite invasive carcinomas must have had the same appearance as the noninvasive areas in the same sections.

The precancerous zones in these 23 sections were compared with lesions in other sections that were composed entirely of atypical cells and lacked cilia. In some cases they were indistinguishable. In others, the lesions in other sections appeared (subjectively) to be less "advanced" than most of those found in the 23 sections with invasive carcinoma. An attempt was made to grade them, but this was very difficult because of the lack of knowledge of the relative importance of various characteristics.

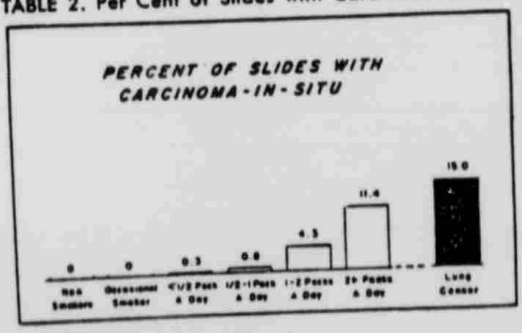
Judging these lesions subjectively from their general appearance, the proportion graded as being most extreme in appearance was much greater among men who died of lung cancer than among cigarette smokers who died of other causes.

The lesions varied in average thickness from 5 cells to a maximum of 38 cells, the majority being about 5 cells in thickness. Of the 23 found in sections, 14 (61%) were 6 or more cells in average thickness. The proportion of such lesions with 6 or more cells in average thickness was 17 per cent among cigarette smokers who died of causes other than lung cancer and 16 per cent among men who died of lung cancer.

Cells with giant nuclei were found in all the 23 lesions in sections with invasive carcinoma, in 76 per cent of those from cigarette smokers who died of causes other than lung cancer, and in 86 per cent of those from men who died of lung cancer.

Our impression is that lesions lacking cilia and composed entirely of atypical cells

TABLE 2. Per Cent of Slides with Carcinoma in Situ.



vary over a continuous scale from least advanced to most advanced rather than fall into several distinctly different categories. Their behavior is, of course, unknown. However, judging from observed morphologic characteristics, we have a strong impression that what we have seen represents basically similar lesions in various stages of progression, which in 23 cases reached the stage of invasive carcinoma before the death of the subject. What proportion would eventually have become invasive if the patient had not died is a matter of conjecture. However, we have the strong impression that all primary bronchial carcinomas pass through an earlier stage in which they have all the characteristics exhibited by the lesions under discussion.

With these considerations in mind we consider it justified to apply the term *precancerous lesion* to all bronchial epithelial tissue composed entirely of atypical cells and lacking cilia. In using this term, we do not mean to imply that, given sufficient time, all such lesions would inevitably become invasive.

Table 2 shows the distribution of cases according to the percentage of sections with precancerous lesions (i.e., areas composed entirely of atypical cells with cilia absent). Once more, precancerous lesions were found in 0 per cent of the 65 men who never smoked regularly, in 4 (11%) of the 36 men who smoked less than ½ package of cigarettes per day, in 15 (25%) of the 59 who smoked ½ to 1 package per day, in 69 (48%) of the 143 who smoked 1 to 2 packages per day, in 27 (75%) of the 36 who smoked 2 or more packages per day, and in 52 (83%) of the men who died of lung cancer. As previously described, the proportion of sections with such lesions increased tremendously with the amount of cigarette smoking.

SUMMARY AND CONCLUSION

Cigarette smoking is the single most important factor in the production of lung cancer in men today. In men who die of lung cancer (squamous and undifferentiated) all of whom were smokers, the remainder of the epithelial lining shows changes that may be considered as preliminary stages to the development of lung cancer, including early invasion. These changes are present in the tracheobronchial tree of individuals who die of causes other than lung cancer. There are few such changes in nonsmokers, but they increase rapidly with the amount of cigarette smoking.

Invasive cancer is present in 23 sections and in all instances merges with an adjoining precancerous lesion (5 or more rows of atypical cells with an absence of cilia). The demonstration of microscopic invasive carcinoma from such precancerous lesions leads us to believe that these can be considered justifiably as truly preinvasive carcinoma.

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