HYPERPLASIA AND METAPLASIA IN THE BRONCHIAL EPITHELIUM

An interim report on research work being carried out by

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INTRODUCTION

THE BELIEF IS steadily gaining ground that most cases of carcinoma of the bronchus are due to the action of noxious substances in the inhaled air upon the bronchial epithelium. If this is true, then it is to be expected that malignant change would be preceded by epithelial hyperplasia similar to that seen in experimental carcinogenesis. Such changes might be looked for in the lungs of established cases of bronchial carcinoma, in the parts remote from the tumour, and also in the lungs of persons dying from other causes who had nevertheless been exposed to atmospheric pollution and cigarette smoke.

This report describes the results of a histological survey of material of these kinds. The first object was to define and classify the abnormalities in the bronchial epithelium, and next to determine their relative frequency, their distribution within the lung and their connexion with chronic bronchitis. Lastly, an attempt has been made to assess their relation to the smoking history.

REVIEW OF PREVIOUS WORK

Squamous metaplasia was the first abnormality to attract attention. It was described as a sequela of influenza (Askanazy, 1919 ; Wegelin, 1942) and in connexion with bronchiectasis and other chronic inflammatory conditions. Lindberg (1935) found transitional (stratified) epithelium in a series of cases of bronchial carcinoma and regarded certain epithelial downgrowths as potentially precancerous. Niskanen (1949) doubted whether squamous metaplasia was a precursor of cancer. Valentine (1957) believed that areas of squamous metaplasia might undergo transformation into carcinoma-in-situ.

Wittekind and Strüder (1953) divided epithelial metaplasia in chronic bronchitis into two types. The changes they describe do not conform to those met with in the present work and their classification has not been found to be applicable.

Weller (1953) distinguished two kinds of change—squamous and transitional metaplasia—and divided both into dormant and proliferative types. His criteria for proliferative activity are very similar to those used by other writers for carcinoma-in-situ, but he saw no metaplastic focus which he was able to diagnose as premalignant, carcinoma-in-situ, or minute carcinoma.

Auerbach *et al.* (1956, 1957), in the preliminary report of a large scale investigation, were the first to describe basal cell hyperplasia and intro-

duced a new classification of the abnormalities seen in bronchial epithelium. This classification is an advance on anything previously proposed and the present work has been based upon it. They found a remarkable parallelism between the incidence of hyperplastic changes and the cigarette consumption and they diagnosed carcinoma-in-situ in a surprisingly large proportion of their cases. Hamilton *et al.* (1957), in a small series of post-mortem cases, reached conclusions similar to those of Auerbach *et al.*

Chang (1957) introduced a method of examining whole mounts of the bronchial epithelium and also cut conventional sections. He drew attention to the frequency of abnormal nuclei in hyperplastic areas, a finding also noted by Bassermann (1957) in smears of bronchial mucus.

MATERIALS AND METHODS

Most of the post-mortem specimens have been obtained at necropsies carried out for H.M. Coroner ; a few were derived from hospitals. No selection has been exercised ; it has, in fact, been difficult to secure an adequate amount of well preserved material because of the rapid post-mortem desquamation of the bronchial epithelium. Fixation within twelve hours of death is essential; when necropsy has to be deferred beyond this time the bronchial tree is filled with formalin injected through the cricothyroid membrane. The lobes of the lung are separated from one another and sliced at right angles to the segmental bronchi. Auerbach *et al.* (1956) cut the entire bronchial tree into blocks—over 200 in all—but we believe that a smaller number (nineteen) provides a representative sample. Of the forty-four post-mortem specimens so far examined, thirty-one were sufficiently well preserved to merit inclusion.

The surgical material consists of lungs or single lobes resected for cancer of the bronchus. Prompt fixation ensures good preservation of the epithelium. Up to the present, sixty-nine specimens have been examined ; smoking histories are available for forty-seven of them.

RESULTS

Before describing the abnormalities met with in the bronchial epithelium it is necessary to mention the cases in which no abnormality was discovered (Fig. 1). Nine of the thirty-one post-mortem specimens came under this heading. One of these was a child of two years ; four were old women who were non-smokers or whose smoking habits were unknown ; and four were old men who had all been smokers. One of the men had smoked twenty cigarettes a day up to his death at eighty from spheroidal cell carcinoma of the bronchus. Two of the others smoked five and sixteen cigarettes a day, while the last, who had given up smoking forty years ago, had an undifferentiated bronchial carcinoma.

Of the forty-seven surgical patients whose smoking histories are known, seven men had normal bronchial epithelium. Their ages ranged from forty-nine to sixty-six years. Three of them had smoked over twenty cigarettes a day for many years.

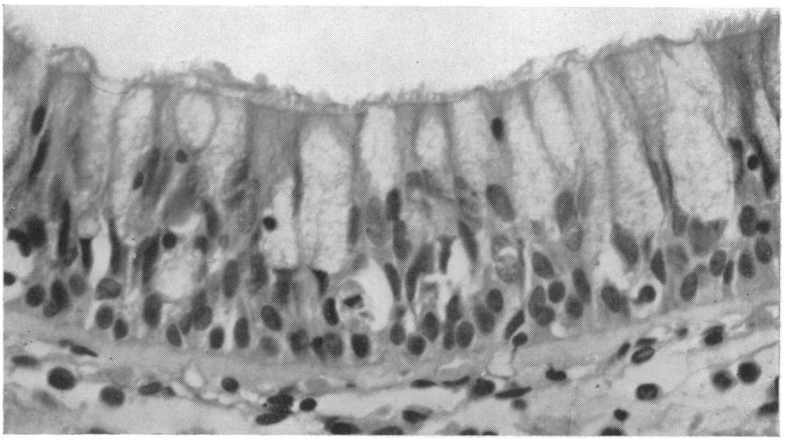

Fig. 1. A woman of sixty-seven whose smoking habits are not known. Section from the left main bronchus. H. and E. × 500. Normal bronchial epithelium with one to two layers of basal cells.

The abnormalities in the bronchial epithelium are classified as follows :

1. Basal cell hyperplasia.
2. Squamous metaplasia.
3. Stratification or transitional change.
4. Epithelial irregularities and carcinoma-in-situ.

1. Basal cell hyperplasia

Multiplication of the layers of the basal cell zone is a common finding (Fig. 2). Although the cells do not lie in regular layers and an exact count is not possible, a useful approximation can be arrived at. We follow Auerbach's (1956) grading :

3-4 layers	—	mild	basal cell hyperplasia
4-6 layers	—	moderate	
7 or more layers	—	advanced	

In the deeper layers the oval nuclei retain their normal perpendicular orientation. Near the surface they become paler and more rounded. These variations are comparatively slight and there is no change in the nuclear-cytoplasmic ratio. Mitoses are very scanty but giant nuclei, usually about twice the size of normal nuclei, are sometimes seen. Giant cells are occasionally found with up to four nuclei of normal size, packed together inside the cell without much increase in cytoplasm. They may occur in comparatively normal epithelium and are not always associated with other nuclear irregularities or with disorganized epithelium.

Basal cell hyperplasia occurs in all parts of the bronchial tree, though it is more frequent and usually more advanced in the larger bronchi. It may be confined to small patches or it may spread uniformly round an entire bronchus.

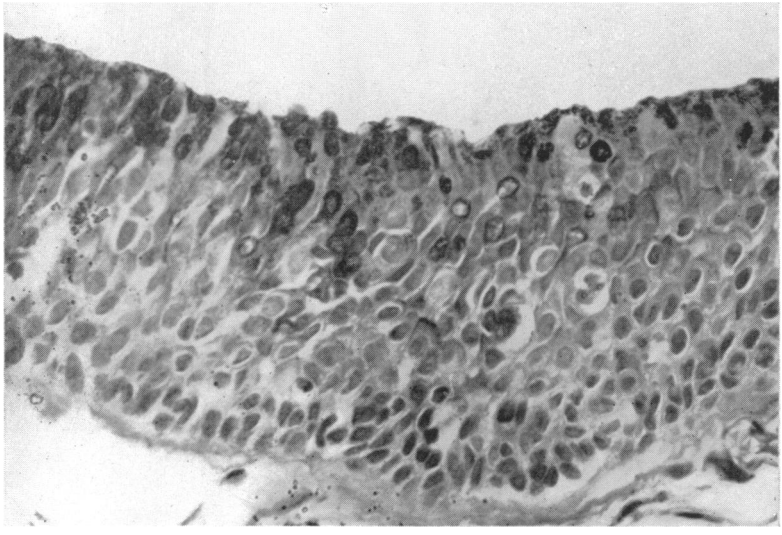

Fig. 2. A man of sixty who smoked twenty to thirty cigarettes a day. Section from the trachea. Periodic acid-Schiff. × 500. Advanced basal cell hyperplasia (up to eight layers of cells) with surviving goblet cells near the surface.

Of the thirty-one post-mortem cases, nine had a mild degree of basal cell hyperplasia. Unfortunately, a smoking history is available for only one of these, a woman of seventy-five who smoked one or two cigarettes a day. Among the four cases with moderate basal cell hyperplasia were a man of seventy-eight who smoked ten cigarettes a day, and a woman of seventy-seven, a non-smoker. The three cases with advanced basal cell hyperplasia were elderly men who smoked sixteen, twenty and twenty to thirty cigarettes a day respectively. Basal cell hyperplasia of some degree was found in twenty-one of the forty-seven surgical cases. In five of them it was mild, in nine moderate, and in seven severe. No correlation with smoking habits was apparent.

2. Squamous metaplasia

This change is quite different from basal cell hyperplasia. The entire thickness of the epithelium is involved and as a rule it resembles the normal stratified squamous epithelium of the mouth or oesophagus. The cells are comparatively large and flattened. The nucleus is large, pale and vesicular. Intercellular bridges are conspicuous and constitute a diagnostic criterion, but keratinization has not been observed. The metaplastic epithelium is often many layers thick and sometimes has papillae which project into the lamina propria. It is more resistant to post-mortem desquamation than normal epithelium.

In distribution squamous metaplasia shows the same centripetal tendency as basal cell hyperplasia but it often occurs in sharply localized

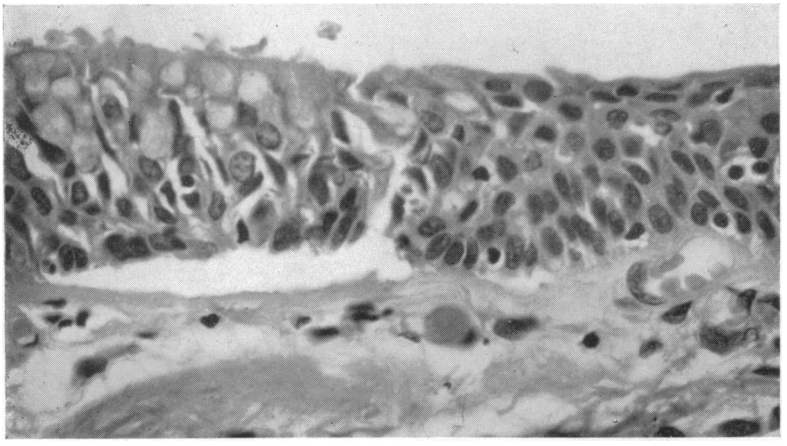

Fig. 3. A man of sixty-six—a smoker. Section from the left upper lobe bronchus. H. and E. ×500. A localised patch of squamous metaplasia, sharply demarcated from normal epithelium.

patches (Fig. 3). It is sometimes confined to the spurs of bifurcations and the crests of longitudinal ridges. The boundary between metaplastic epithelium and the adjacent normal epithelium is often quite abrupt. The lamina propria beneath patches of metaplastic epithelium often shows evidence of chronic inflammation : fibrosis, infiltration with lymphocytes, and increased vascularity.

Squamous metaplasia was present in ten of the thirty-one post-mortem cases. No correlation with age, severity of bronchitic changes, or smoking history is yet apparent from these small numbers, but it is noteworthy that in the three cases with severe basal cell hyperplasia squamous metaplasia was found in addition.

It was present in twenty-five of the forty-seven surgical cases ; in some of these it was very mild. Three of them were pipe smokers ; the cigarette consumption of the others ranged from six to fifty a day. Most of them showed mild bronchitic changes, but there was no obvious association between squamous metaplasia and chronic bronchitis.

3. Transitional change

Certain intermediate types, difficult to classify, are found in a few cases. In these the epithelium is several layers thick, the superficial layers being stratified while the deep layers retain the usual characters of basal cells. The columnar cell layer is absent : this point can be verified by staining with periodic acid-Schiff to reveal any remaining goblet cells. Sometimes the appearance of urinary epithelium is closely simulated. Intercellular bridges and other features of squamous epithelium are lacking.

The nature of this change is obscure. In some cases it probably represents basal cell hyperplasia in which the columnar cells have been lost. In others it may be a precursor of squamous metaplasia.

Transitional change of this type has been observed in six of the post-mortem cases, usually only in small areas. No correlation with the factors previously considered is apparent. It has been observed in ten of the surgical cases, in continuity with areas of squamous metaplasia.

4. Epithelial irregularities and carcinoma-in-situ

Disorganized epithelium has so far been observed in a few cases, in none of which it fulfils all the criteria of carcinoma-in-situ (Fig. 4). In our examples the nuclei are hyperchromatic and vary in size and shape, but there is still some cellular differentiation and only a few mitoses are apparent. Sometimes multiple nucleoli are present; the significance of this change is not clear.

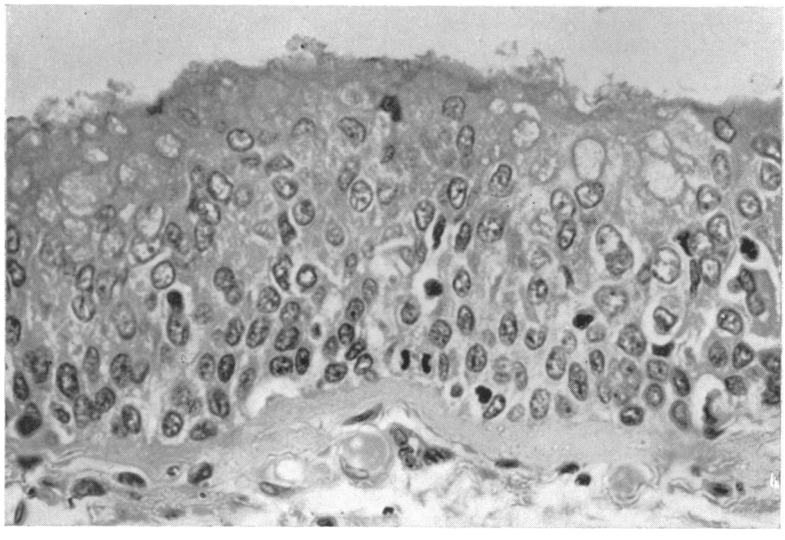

Fig. 4. A man of fifty-five who smoked fifteen cigarettes a day. Section from the carina. H. and E. ×500. A patch of irregular epithelium with a mitosis.

In the thirty-one post-mortem cases epithelial irregularities of this kind have been observed in three; among the forty-seven surgical cases, in four only.

DISCUSSION

The number of cases so far available is too small to permit definite conclusions to be drawn, but it is already evident that changes of all the kinds described by previous workers are to be found in our material and some provisional interpretations are possible.

The bronchial epithelium may be perfectly normal in heavy smokers, even in men who have smoked from adolescence and reached a consumption of forty cigarettes a day. It is also clear that the epithelium in the neighbourhood of a bronchial carcinoma may be normal. Nevertheless, epithelial abnormalities are common in both these conditions and it seems possible that a more detailed search might reveal abnormalities which are overlooked if only a few blocks are taken.

Basal cell hyperplasia is a common and conspicuous change. There is often a similarity between the hyperplastic basal cells and the cells of oat cell carcinomas. Whether this is more than a superficial resemblance remains to be proved. We have found nothing to contradict Auerbach's (1956) suggestion that basal cell hyperplasia is connected with cigarette smoking.

The frequency of squamous metaplasia has long been recognized and our observations have so far provided nothing new. We agree with Weller (1953) that patches of squamous metaplasia vary in activity, some being dormant while others show vigorous proliferative changes. It is possible that the latter may be precancerous.

Basal cell hyperplasia and squamous metaplasia tend to be centripetal. In many specimens these changes are most advanced at the carina, rather less severe in the main bronchi and progressively less intense in the lobar and segmental bronchi. This pattern is in accordance with the work of Macklin (1956) who showed that although the entire tracheobronchial tree is vulnerable to noxious substances in the air, the parts exposed to the most concentrated and sustained attack are the large bronchi near the carina.

We have seldom observed changes which could be regarded as intermediate between basal cell hyperplasia and squamous metaplasia, and we have never met with appearances which we interpreted as indicating a transition from one type to the other. As a working hypothesis, we regard the two types of change as differing in kind and not merely in degree. In the hope of throwing further light on the differences between them, we are paying special attention to nuclear structure and applying histochemical methods to some of our material.

The nature of transitional change is still obscure, but the absence in epithelial activity makes it unlikely that it plays any important part in the genesis of cancer.

We cannot confirm Auerbach's (1956, 1957) findings on the frequency of carcinoma-in-situ. We have found areas showing intense proliferative changes but in none of them have we been satisfied that all the criteria of carcinoma-in-situ have been fulfilled. Nevertheless, in border-line cases the diagnosis is open to differences of opinion and our disagreement is probably one of interpretation rather than observation.

In conclusion, it has become apparent that the responses of bronchial epithelium to noxious stimuli are comparatively restricted and we have

reached a stage in the work at which we expect to observe no new histological abnormalities. Our remaining task is to collect enough material to enable us to analyse the changes in greater detail and to extend our observations by certain histochemical techniques ; these are already under trial.

ACKNOWLEDGMENTS

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APPOINTMENT OF FELLOWS AND MEMBERS TO CONSULTANT POSTS

D. G. JAMES, M.D., M.R.C.P., M.R.C.S.	Consultant Physician to Royal Northern Hospital.
J. N. ASTON, M.B., F.R.C.S.	Consultant Orthopaedic Surgeon to Mount Vernon Hospital.
W. BRUMFITT, M.B., M.R.C.P., M.R.C.S.	Consultant Clinical Pathologist to Edgware General Hospital.
I. YENTIS, M.D., M.R.C.P., F.F.R.	Consultant Radiologist to Windsor Group of Hospitals.
K. TILL, M.B., F.R.C.S.	Consultant Surgeon to the Hospital for Sick Children, Great Ormond Street.

The Editor is always glad to receive details of new appointments obtained by Fellows and Members, either through the Hospital Boards or direct.

RECENT OVERSEAS VISITORS TO THE COLLEGE

RECENT OVERSEAS VISITORS to the College have included Mr. and Mrs. M. P. Susman from Sydney, who attended the monthly dinner in April.