THE IMPORTANCE OF EPIDERMOID CARCINOMA *IN SITU* IN THE HISTOGENESIS OF CARCINOMA OF THE LUNG

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IN ATTEMPTING to reconstruct the histogenesis of disease processes, the study of advanced stages has generally been unrewarding. This has been true of carcinoma of the lung. However, occasional examples of early neoplasia have been observed which suggest the mode of origin of certain pulmonary tumors. The reporting of such isolated observations appears justified, since a better understanding of carcinogenesis in the lung may be anticipated from the summation and synthesis of a greater experience with such early lesions.

Gray and Cordonnier[7] must be credited with the first description of a minute peripheral bronchogenic carcinoma. The tumor they described was asymptomatic and found incidentally at postmortem. It arose as a superficial papillomatous growth in the ductus alveolaris, measured less than 1 mm. in diameter, and yet had produced lymphatic invasion. Womack and Graham[30, 31] have described small islands of "epithelial metaplasia" associated with congenital cystic lesions of the lung. Five additional minute peripheral pulmonary carcinomas showing invasive properties are reported by Peterson *et al.*[22] Karsner and Saphir[10] and Spain and Parsonnet[25] have recorded cases in which multiple microscopic sites of origin of an undifferentiated peripheral neoplasm were found. We have also recently observed evidence of multiple sites of origin in a peripheral bronchogenic carcinoma. The chief lesion in our case was an undifferentiated epidermoid tumor of varied pattern located in the periphery of the right upper lobe. The lower and middle lobes of the same lung were honeycombed with cystic spaces, scattered through which there were islands of epithelial metaplasia (Fig. 1). These cellular areas were free of mitotic figures, were located outside the bronchi, and did not show invasion or other evidence of carcinoma. We believe, however, that such areas could become invasive carcinoma. Spain and Parsonnet's case supports this assumption. Our patient, who was 48 years old at the time of right pneumonectomy, is alive and well without evidence of any difficulty in the opposite lung two years later.

The above cases suggest the method of origin of at least some of the peripheral tumors of the lung. In tumors arising in the major bronchi, we have been impressed with the frequent association of the triad: squamous metaplasia of the bronchial epithelium, epidermoid carcinoma *in situ*, and frank invasive epidermoid or undifferentiated carcinoma of the lung. We believe that such an intra-epithelial method of origin is common in bronchogenic carcinoma.

The discovery of intra-epithelial cancer in the bronchus should excite no surprise, since many examples of non-invasive malignancy have been reported in various other organs. Adenocarcinoma *in situ* has been described in the stomach,[15] large bowel, appendix,[16] breast,[4] and endometrium.[8] Other

organs lined by squamous epithelium such as the skin,[2, 18] oral cavity, larynx,[5] esophagus, kidney,[3] vulva,[9, 11] and uterine cervix[6, 23, 27, 29, 32] have been found to give rise to non-invasive epidermoid carcinomas. The most extensive studies of this type of lesion have been made in the cervix, and in this organ intra-epithelial carcinoma has been unquestionably linked with the invasive cancer.

Several investigators, working independently, have enumerated the following stages of development of epidermoid carcinoma of the cervix from a study of serial biopsies over a period of several years: (1) normal squamous epithelium, (2) hyperactivity of the basal cell layer, (3) epidermoid carcinoma *in situ*, and (4) invasive epidermoid carcinoma.

The evidence on which this synthesis is based is contained in the following observations: Younge[32] reported 15 cases in which intra-epithelial "anaplasia" (equivalent to advanced basal cell hyperactivity in our terminology) has been followed by epidermoid carcinoma *in situ; in situ* carcinoma is commonly found at the periphery of invasive carcinoma of the cervix; the site of predilection for both is the same (junction of the columnar with the squamous epithelium in the cervical canal); and a total of about 30 cases have been described[23, 27, 32] in which carcinoma *in situ* of the cervix has been followed by invasive carcinoma. These observations are well documented and reported independently by qualified investigators, so that there can be little doubt that in the cervix, at least, this progression from basal cell hyperactivity to carcinoma *in situ* to invasive cancer exists.

Although others[1, 7, 20, 21, 24] have previously described epidermoid carcinoma *in situ* in the bronchial epithelium in isolated cases, the relatively frequent occurrence of this finding in association with frankly invasive carcinoma has not been stressed. We have reviewed the microscopic sections of 60 recent cases of epidermoid and undifferentiated carcinoma of the lung removed at operation and have found unquestionable carcinoma *in situ* in 13 (22 per cent) and anaplastic hyperactivity of the intact bronchial epithelium in eight additional cases, or 13 per cent. Thus, in 35 per cent of the cases reviewed, either marked anaplasia of the intact epithelium or frank carcinoma *in situ* was found adjacent to invasive carcinoma of the lung. In all of these the tumor was central in origin, arising in lobar bronchi or in one of their major segmental divisions. In addition, in all but seven (11.7 per cent) of the 60 cases, advanced squamous metaplasia of the bronchial epithelium was found. It should be emphasized that the microscopic sections reviewed were for the most part random ones and no consistent attempt had been made to demonstrate the epithelial changes at the periphery of the tumors. We therefore believe that a more intensive search might well reveal an even higher incidence of intra-epithelial cancer.

The association of marked squamous metaplasia of the bronchial epithelium and ducts of the mucous glands with carcinoma of the lung has previously been noted.[12-14, 19, 20, 28] The mere occurrence of squamous metaplasia in association with carcinoma of the lung, however, cannot be regarded as anything more than an interesting coincidence, since a similar transformation from the tall, single-layered, columnar bronchial epithelium to stratified squamous epithelium has been observed repeatedly in a large variety of chronic pathologic processes in the lung. Prominent among these are severe bronchiectasis (Fig. 2), lipoid pneumonia, tuberculosis, and chronic lung abscess. It is common knowledge that these lesions are only rarely precursors of carcinoma of the lung.[28]

Although squamous metaplasia alone probably does not give rise *shui generis* to frank bronchogenic carcinoma, we have

FIG. 1

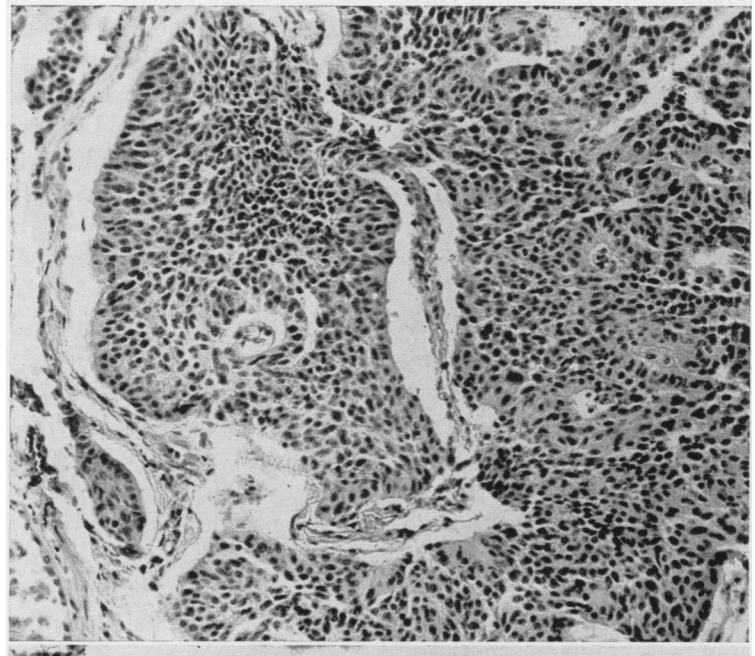


FIG. 2

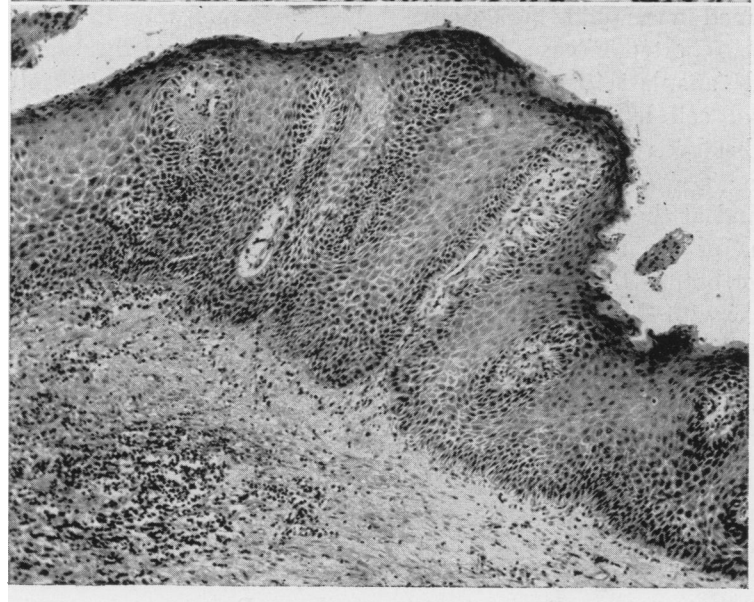


FIG. 1.—Photomicrograph. A focal area of atypical epithelium at a considerable distance from the carcinoma in the right upper lobe (x 180).

FIG. 2.—Photomicrograph. Advanced squamous metaplasia in bronchiectasis (low power).

learned to associate increased activity of the vasal cell layer with frank invasive carcinoma at some nearby site in a significantly large number of cases. The first change in this process is increased mitotic activity of the basal cell layer, which leads to more dense packing of the nuclei, increased stratification, and resultant thickening of the

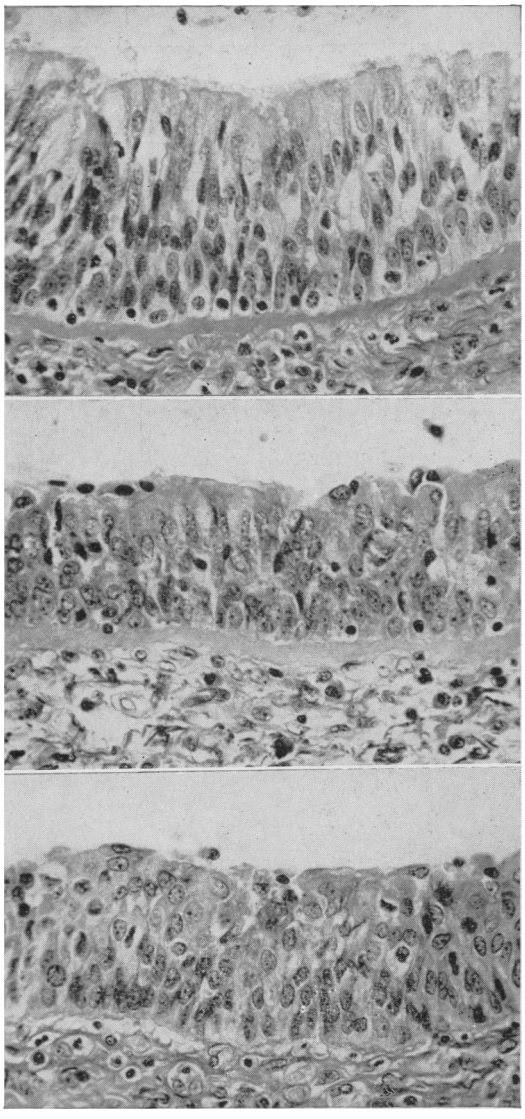


FIG. 3.—(Top) Photomicrograph. Early stage of basal cell hyperactivity with persistence of mucous-secreting cells and ciliated cells (x 310).

FIG. 4.—(Center) Photomicrograph. More advanced hyperactivity with loss of stratification and beginning disappearance of cilia. Basement membrane intact (x 310).

FIG. 5.—(Bottom) Photomicrograph. Hyperactivity extending into all layers of the epithelial lining (x 310).

epithelial layer. The cells are all of normal size and nuclear ratio and the superficial layers of the mucosa retain their cilia and other normal characteristics (Fig. 3). As the process becomes more advanced the mitotic activity increases, and the nuclei become more rounded and more densely packed as the basal cell activity extends closer to the surface (Fig. 4). Finally all layers are involved (Fig. 5) and none of the ciliated superficial layer remains. Complete epidermidalization with intra-epithelial pearls and marked irregularity of the nuclei is probably the stage just before transformation into a frank epidermoid carcinoma *in situ*. All of the above illustrations are taken from bronchial epithelium immediately adjacent to frank carcinomas of the lung.

The criteria we have used to identify carcinoma *in situ* in the bronchus are as follows (Figs. 6, 7):

1. Absence of cellular differentiation (mucous-secreting cells and ciliated border) and organization.
2. Variation in size and shape of the nuclei with nuclear hyperchromatism.
3. Increase of the nuclear-cytoplasmic ratio.
4. Increased number and abnormal forms of mitotic figures.
5. Above changes seen extending through all layers to the surface.
6. Intact basement membrane.

In contrast to the above picture, the areas of simple basal cell hyperactivity show some stratification and organization of the nuclei, normal-appearing and constant sized nuclei, and infrequent mitotic figures. It should be emphasized that quite active changes may be found in the deeper layers in basal cell hyperactivity but they do not extend through the entire epithelial membrane.

In order to illustrate the progressive stages of this process we have chosen a single area from a lung bearing an undifferentiated carcinoma. The abrupt transitions

from basal cell hyperactivity to epidermoid carcinoma *in situ* to anaplastic carcinoma are clearly seen (Figs. 8, 9, 10). Similar changes to carcinoma *in situ* may occur in the surface epithelium abruptly from essentially normal epithelium (Fig. 11) and also may extend down the ducts of mucous glands (Fig. 12). In other areas the glands themselves may contain intra-epithelial cancer and, as seen on the surface, this change may take place abruptly from otherwise normal epithelium. The surrounding glands in these areas are frequently normal, although some may become distended because of obstruction from an overlying carcinoma *in situ*. The presence of malignant transformation of the glandular epithelium does not represent true invasive carcinoma (as argued by TeLinde in the case of carcinoma of the cervix) for the basement membrane is still intact, and although the glands may become wholly plugged with tumor, continuity with the surface carcinoma can be demonstrated by serial sectioning.

In all the above illustrations intra-epithelial carcinoma of the bronchus has been found at the periphery of a clinically obvious invasive carcinoma of the lung. A particularly disturbing feature of this process, however, is the occurrence of multiple areas of preinvasive malignant change at some distance from the tumor. In one case a small locally invasive epidermoid carcinoma of the right upper lobe bronchus was found, but skin areas of carcinoma *in situ* with intervening normal mucosa were discovered extending up to the line of transection of the bronchus. This situation is reminiscent of the multiple sites of origin of epidermoid carcinoma of the oral cavity and raises the question of whether similar changes exist in the trachea, opposite lung, and other portions of the lower respiratory tract.

In two cases, at least, we have been able to demonstrate the existence of carcinoma *in situ* in the lung opposite the main tumor. In the first of these the roentgenogram revealed bilateral hilar enlargement with a 6 cm. mass in the posterior portion of the *left* lower lobe. On bronchoscopy, blunting of the spur of the *right* middle lobe was seen and a biopsy taken from this area revealed epidermoid carcinoma *in situ* (Fig. 13). An aspiration biopsy of the mass in the *left* lower lobe demonstrated undifferentiated epidermoid carcinoma (Fig. 14).

The second case manifesting this widespread distribution of intra-epithelial cancer was even more striking and suggests the possibility of pre-invasive changes in the bronchial epithelium for considerable pe-

FIG. 6

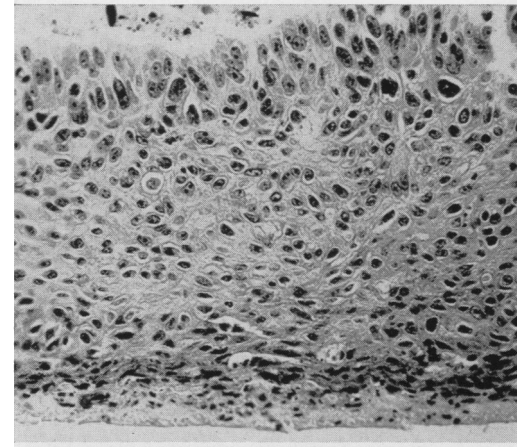
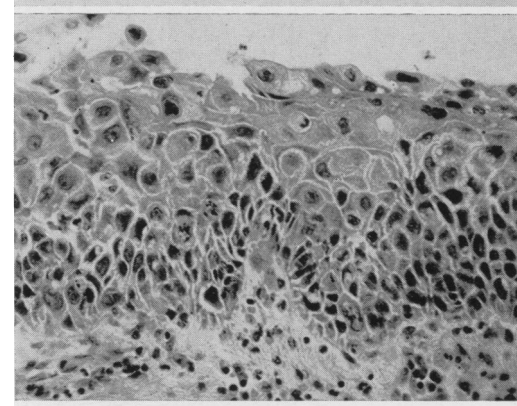


FIG. 7



FIGS. 6 and 7.—Photomicrographs. Two stages of epidermoid carcinoma *in situ*. Figure 6 shows intercellular bridges. Note variation in size and shape of nuclei and hyperchromatism which is extending through all layers (x 210).

FIG. 8

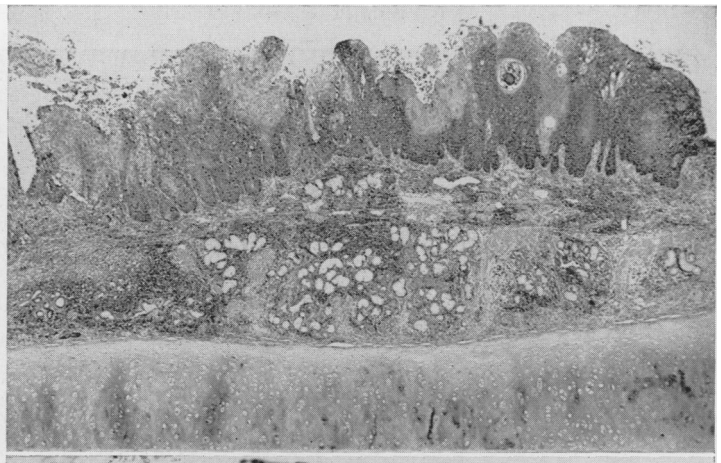


FIG. 9

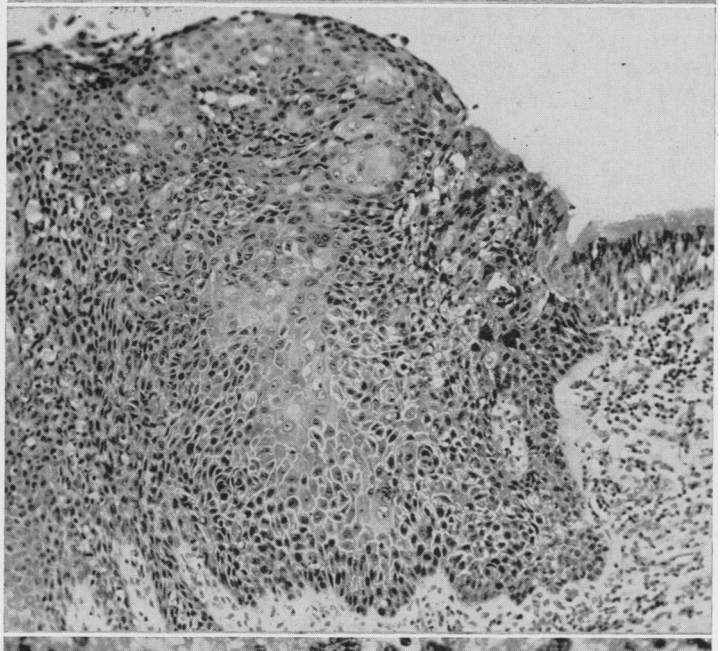


FIG. 10

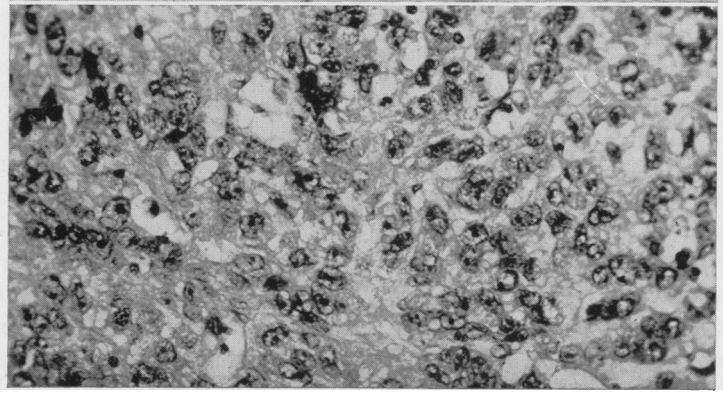


FIG. 8.—Photomicrograph to show abrupt transition from squamous metaplasia of lining epithelium on the right to epidermoid carcinoma *in situ* in the center and undifferentiated tumor on the far left.

FIG. 9.—Photomicrograph. High power view of the zone of transition to carcinoma *in situ*.

FIG. 10.—Photomicrograph of an area of undifferentiated infiltrating tumor on the far left.

FIG. 11

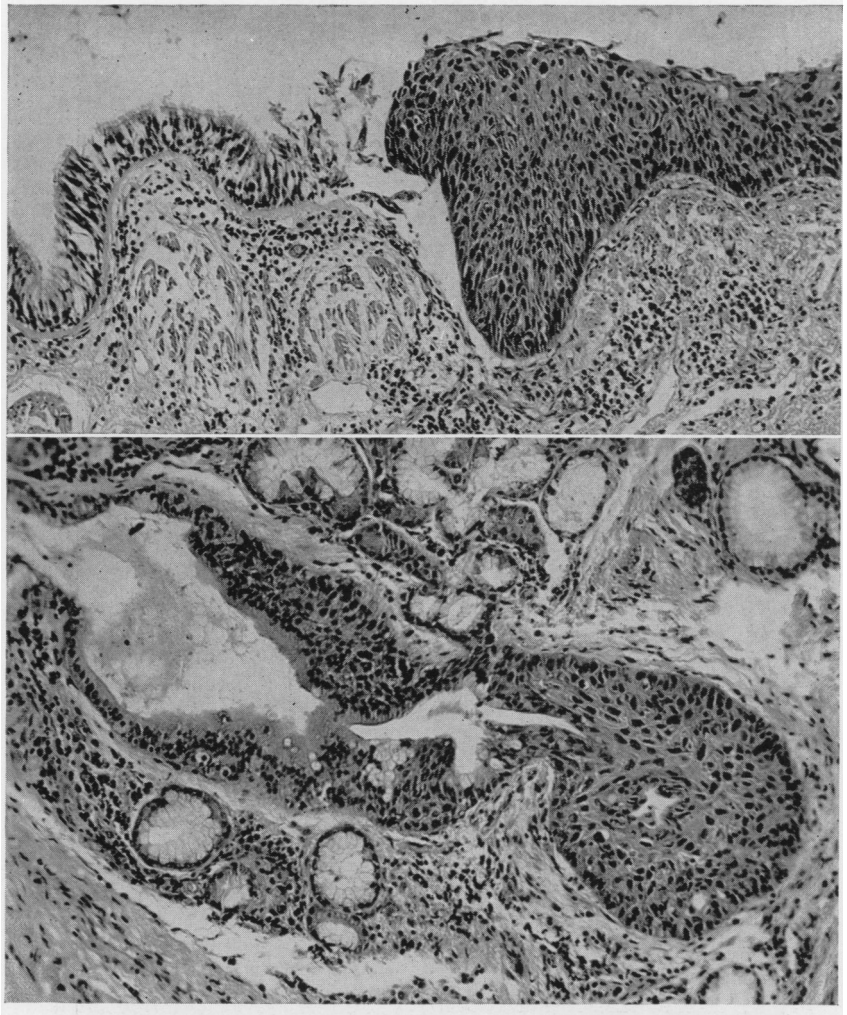


FIG. 12

FIG. 11.—Photomicrograph. Note sharp transition between carcinoma *in situ* and normal lining epithelium (x 110).

FIG. 12.—Photomicrograph. Extension of carcinoma *in situ* down mucoid gland ducts. Basement membrane remains intact (x 150).

riods before the basement membrane is violated. This 68-year-old male had a chronic productive cough with blood-streaking for nine months before presenting himself for treatment. Bronchoscopy was negative, but cytologic examination of bronchial secretions and sputum were positive for cancer cells. Because of a left hilar mass visualized by roentgenogram, a left pneumonectomy was done. In the gross specimen, irregular raised areas on the mucous membrane extending right up to the line of transection were found (Fig. 15). Similar but more marked thickening of the mucosa of the upper and lower lobe main bronchi were found, but no frank tumor mass. Microscopic sections of all the areas, including those in the main stem bronchus, revealed florid epidermoid carcinoma *in situ*. This man died six months after operation and at

FIG. 13

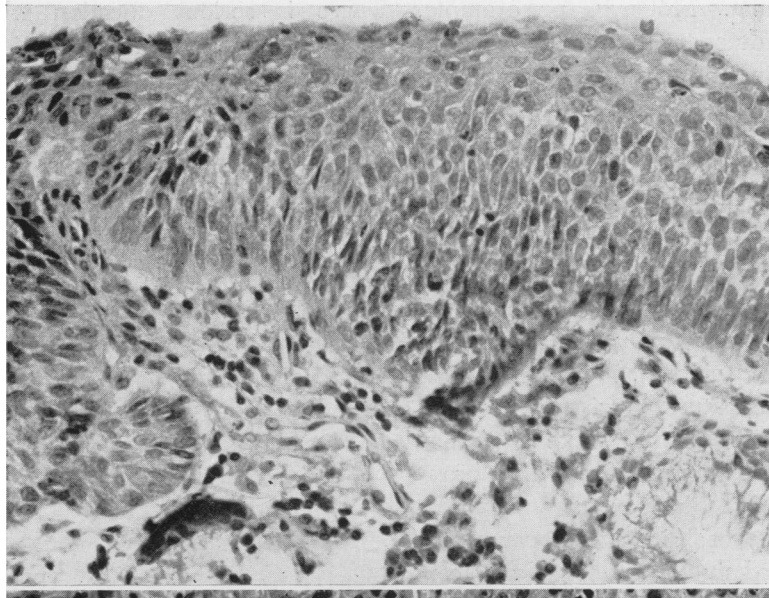


FIG. 14

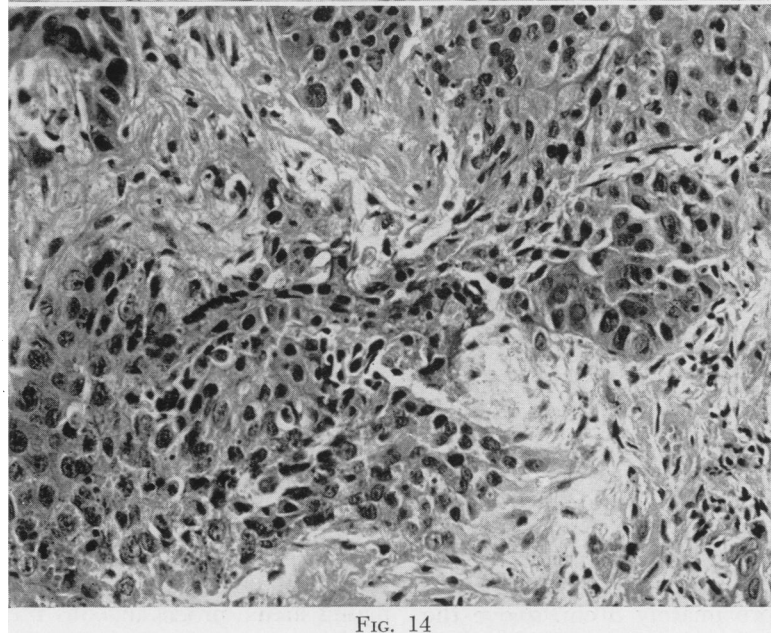


FIG. 13.—Photomicrograph of bronchoscopic biopsy taken from *right middle lobe*, showing epidermoid carcinoma *in situ* (x 310).

FIG. 14.—Photomicrograph. Same case as illustrated in Figure 13. Aspiration biopsy from mass in *left lower lobe* showing undifferentiated epidermoid carcinoma (x 310).

postmortem examination extensive intra-epithelial cancer in the opposite lung, as well as large masses of anaplastic tumor invading the mediastinal structures, were found.

The validity of all the above observations in the last analysis rests on the strength of circumstantial evidence. In animal experimentation, however, the whole process has been traced through identical stages from

its inception in squamous metaplasia to frank carcinoma. Möller,[17] for example, found that pulmonary tumors induced in mice by painting the skin with tar were preceded by "papilloma-like modifications on the bronchi. . . . The next stage was epithelial metaplasia followed by tumor formation." Niskanen,[20] working with rats injected intratracheally and subcutaneously with 1:2:5:6-dibenzanthracene, describes a metaplastic regeneration of the bronchial epithelium which eventually leads to frank squamous cell carcinoma.

The question naturally arises as to what interpretation one should make if epidermoid carcinoma *in situ* is found in a bronchoscopic biopsy. Three major possibilities suggest themselves: (1) The biopsy represents an isolated single area of early cancer; (2) it is one of several similar areas of intra-epithelial cancer; or (3) the *in situ* carcinoma lies next to a frank invasive carcinoma. If the clinical factors such as history, radiologic findings, and gross bronchoscopic appearance are in favor of the last possibility, we feel that one is justified in performing an exploratory thoracotomy without the necessity of further confirmatory evidence. Such a situation arose recently in a 52-year-old man with a five-month history of hemoptysis and moderate increase in his chronic cough. A bronchoscopic biopsy (Figs. 16, 17) revealed epidermoid carcinoma *in situ* of the surface epithelium and mucous gland ducts. At operation a 3.5 cm. tumor mass in the apical segment of the left lower lobe was found. Although the bronchus was transected approximately 5 cm. above the palpable mass, carcinoma *in situ* without violation of the basement membrane was found extending proximally to within a few millimeters of the line of transection.

This experience, together with the frequent occurrence of carcinoma *in situ* in the lungs we have examined, has led us to the conclusion that there is almost invariably an invasive carcinoma nearby if the biopsy shows an intra-epithelial cancer. There is serious question whether one should ever treat a bronchogenic carcinoma by lobectomy if carcinoma *in situ* has been demonstrated, even though at the time of operation the lymph nodes are proved negative. In addition to the cases of extensive surface involvement mentioned above, one case in particular that we have observed

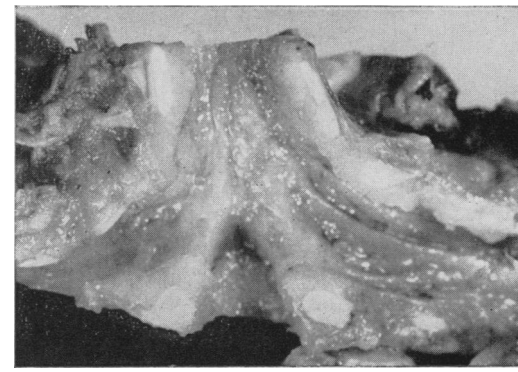


FIG. 15.—Gross photograph of left main stem bronchus showing isolated areas of carcinoma *in situ* extending from the upper lobe bronchus up to the line of transection. Carcinoma *in situ* found in the stump of this bronchus at postmortem and in the opposite lung.

supports this contention. In this individual a carcinoma clinically limited to the right upper lobe was found, but in the lung subsequently removed at operation widespread carcinoma *in situ* extending down into the intermediate bronchus was demonstrated. All of the regional lymph nodes in this case were free of metastases on microscopic examination. Obviously, palpation at the time of operation would be of no value in recognizing such a process.

In those cases in which the biopsy shows considerable basal cell hyperactivity and anaplasia, strong suspicion that a carcinoma is present should be entertained and renewed efforts made to demonstrate its presence. Of considerable help in such cases is the cytologic examination of the sputum. In the 13 cases of carcinoma of the lung mentioned earlier in which epidermoid carci-

FIG. 16

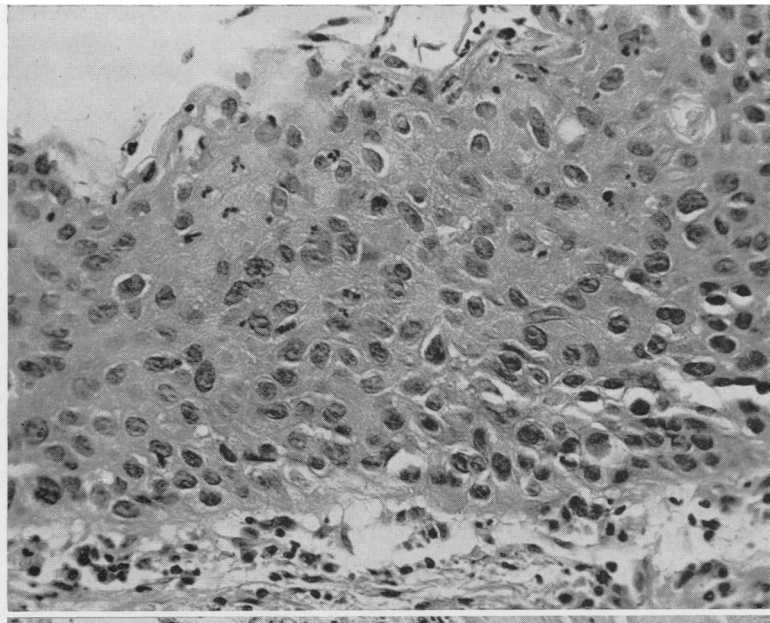
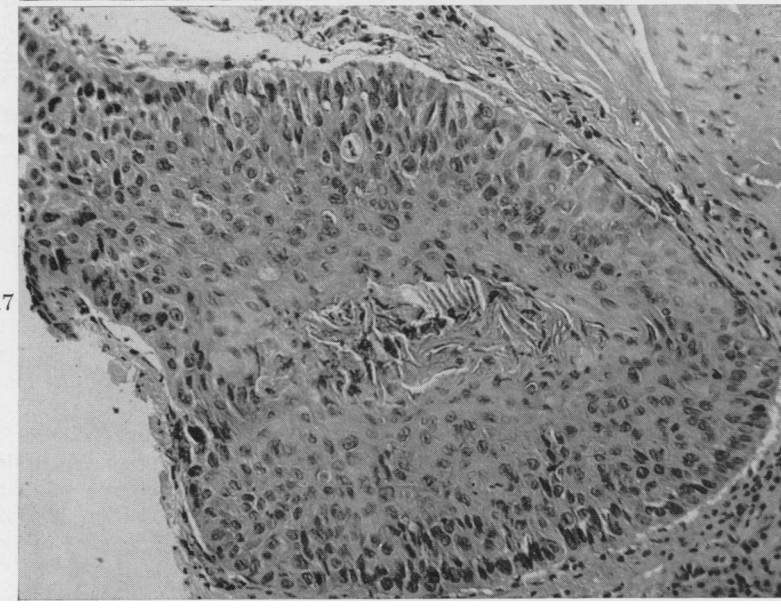


FIG. 17



FIGS. 16 and 17.—Photomicrographs. Bronchoscopic biopsy showing epidermoid carcinoma *in situ* of the surface epithelium and the mucous gland ducts. Invasive carcinoma of the lung found at operation (x 300, x 180).

noma *in situ* was associated, a positive cytologic diagnosis was made in ten, two were highly suspicious, and only one was negative. This last case had an inadequate number of examinations (one sputum and one bronchial washing) and the sputum was markedly purulent in addition—a factor frequently interfering with the accuracy of the cytologic examination. This high incidence of positive results compares favorably with the report of Graham,[6] who found in her own experience and in the published liter-

ature that of 210 cases of carcinoma *in situ* of the uterine cervix, 189 (90 per cent) were positive on cytologic examination of the vaginal secretions.

A recent case illustrates the advantage of the cytologic method in addition to the finding of advanced basal cell hyperactivity in the bronchoscopic biopsy. The roentgenologic findings of diffuse infiltrates in the right upper lobe in addition to the history of productive cough, weight loss, and weakness, suggested the need for surgical exploration on this man. With the chest open a definite diagnosis of cancer could not be made even after biopsy of the hilar mass. On the basis of two positive cytologic examinations and the hyperplasia in the bronchoscopic biopsy, a pneumonectomy was done. Examination of the specimen revealed an undifferentiated carcinoma arising in the right upper lobe. At the point of origin of the tumor, the metaplastic epithelium made an abrupt change to carcinoma *in situ*.

SUMMARY AND CONCLUSIONS

In a study of human cases of carcinoma of the lung, evidence has accumulated that epidermoid and undifferentiated tumors of the major bronchi may arise first as islands of carcinoma *in situ*. The initial stage in this process is a progressive metaplasia of the surface epithelium with cellular hyperactivity in the basal layer. Statistically speaking, this process appears to be an important one, since examples of it were found in 35 per cent of 60 unselected epidermoid carcinomas of the lung. Epidermoid carcinoma *in situ* may be present at the periphery of an invasive tumor or appear at multiple sites either in the same lung or in other portions of the tracheobronchial tree. The discovery of such a process almost invariably indicates an invasive tumor nearby and indicates an aggressive therapeutic approach. In a high percentage of such cases the cytologic examination of the sputum will substantiate the diagnosis.

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