clinically and radiologically, was virtual complete resolution. It is, however, recognized that bone destruction and joint involvement can give rise to deformity and disability in the vaccinal as well as the variolar form of osteitis.

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CLINICAL EVALUATION OF CYTODIAGNOSIS IN BRONCHIAL CARCINOMA

BY

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The first convincing account of the identification of malignant cells in sputum was given by Hampeln (1887), and by the end of the nineteenth century textbooks on laboratory techniques contained chapters on cytodiagnosis. At the beginning of this century sporadic papers appeared describing success in single cases, but Hampeln (1919) was the first to publish an objective assessment of the value of cytology in the diagnosis of bronchial carcinoma, recording 13 successes in a series of 25 cases.

Cytodiagnosis, however, did not become popular, the main disadvantages being loss of translucency and cellular distortion which occurred during the drying of smears rich in mucus. These difficulties were largely overcome by the introduction of wet fixation in alcoholic solutions (Dudgeon and Patrick, 1927). During the next 16 years important papers appeared in Britain stressing the value of sputum cytology (Dudgeon and Wrigley, 1935; Roodhouse Gloyne, 1937; Barrett, 1938; Gowar, 1943); and, in Denmark, Wandall (1944) published an authoritative monograph on neoplastic cells in sputum.

The vital phase of development occurred in America following the publication by Papanicolaou (1942) of his staining technique and in the following year of the classical monograph on the diagnosis of uterine cancer by vaginal smear (Papanicolaou and Traut, 1943). This stimulated extensive research in other fields of cytology, and during the 1940s many papers appeared confirming its value in the diagnosis of bronchial carcinoma; the percentage of positive findings varied from 55% (Farber *et al.*, 1950) to 80% (Herbut and Clerf, 1946).

In the United States, pulmonary cytodiagnosis soon became a routine procedure, largely because of the endorsement and support of the American Cancer Society and the United States Public Health Service (Papanicolaou, 1958).

Although so much of the pioneer work had been done in Britain, little attention was paid to the method until recent years, and, indeed, it is still regarded in some quarters as an expensive, time-consuming, and somewhat unreliable technique.

Material and Methods

The aim of the present study is to evaluate cytodiagnosis carried out as a routine procedure in a thoracic surgical unit served by a general laboratory.

During a two-year period cytodiagnosis was employed in 470 consecutive cases of suspected bronchial carcinoma.

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The diagnosis was confirmed in 240 cases, 202 (84%) of which were histologically proved; the remainder followed a typical malignant course to death.

We have analysed these 240 cases and have attempted to elucidate the following points: (1) comparison of cytodiagnosis with other diagnostic methods available; (2) the relative efficiency of the various methods of collecting specimens for cytological examination; (3) factors affecting the exfoliation of tumour cells; and (4) the causes of "false-positive" results.

Conventional Diagnostic Methods.—In addition to routine clinical and radiological examination, tomography was frequently employed. In practically every case bronchoscopy was performed, with biopsy of any abnormal tissue seen. When bronchoscopy was negative a bronchogram was done. Biopsy of scalene nodes, pleura, or distant metastases was carried out in a few cases.

Cytodiagnostic Methods

The following specimens were examined.

Sputum.—Three adequate samples were requested, but it was not always possible to obtain these, as treatment of the patient was never delayed in order to obtain a full cytological examination.

Bronchial Aspirate.—This was collected at bronchoscopy with the Mullard (1958) specimen-collector manufactured by Allen and Hanburys.

Bronchial Smears.—These were taken direct from suspicious areas seen at bronchoscopy.

From each specimen two slides were made and stained by the Papanicolaou method. The cells were graded according to Papanicolaou's criteria as follows:

Unsatisfactory Sample.—No report.

Negative.—Class 1 or class 2 cells present. Class 1 cells are normal sputum components. Atypical (class 2) cells are often found in inflammatory lung conditions.

Suspicious.—Class 3 cells present. In our experience 50% of the patients producing these cells eventually prove to have a carcinoma. This agrees with the findings of Rome and Olson (1957).

Positive.—Class 4 or class 5 cells present. Class 4 cells are highly suspicious of malignancy, but there is a slight element of doubt, especially in view of the bizarre appearances which may occur in squamous metaplasia. Class 5 cells are regarded as being as definite a proof of malignancy as a positive biopsy.

Umiker (1961) claims that large peripheral tumours exfoliate more readily than smaller ones, the critical diameter being 5 cm. In this series we found that of 55 measurable peripheral tumours 24 were over 5 cm. in diameter and 31 were 5 cm. or less. Cytodiagnosis was positive in 46% of the larger tumours and 42% of the smaller. We therefore cannot agree with Umiker's findings.

Position of Tumour in Lung

Our results are set out in Table VI. Our experience agrees with those authors who have found a higher proportion of positive results in hilar than in peripheral tumours (Woolner and McDonald, 1949; Ackerman and Spjut, 1960; Umiker, 1961) and in lower lobe than in upper lobe tumours (Buffmire and McDonald, 1951; Spjut *et al.*, 1955; Umiker, 1961).

TABLE VI.—*Relationship of Positive Cytodiagnosis to Position of Tumour*

Position of Tumour	No. of Cases	Cytodiagnosis Positive
Hilar or hilar and peripheral ..	183	125 (68.3%)
Peripheral	57	24 (42.1%)
Main stem bronchus	62	50 (80.6%)
Lower lobe	65	43 (66.1%)
Upper	113	56 (49.6%)

Histological Type

We have found that anaplastic tumour cells are less often identified in the sputum than in the bronchial aspirate and smear, while squamous cells are more readily discovered in the sputum. This is shown in Table VII, where the cell type identified in histological preparations is compared with that found in sputum, bronchial aspirate, and bronchial smear.

TABLE VII.—*Comparison of Histological and Cytological Cell Type*

Cell Type	Histology (202 Cases)		Sputum (79 Positives)		Bronchial Aspirate (85 Positives)		Bronchial Smear (87 Positives)	
	No.	%	No.	%	No.	%	No.	%
Anaplastic	83	41.1	32	40.5	47	55.3	58	66.7
Anaplastic and squamous ..	50	24.7	1	1.3	2	2.4	1	1.1
Squamous	55	27.2	39	49.4	33	38.8	24	27.6
Adenocarcinoma ..	14	7.0	7	8.8	3	3.5	4	4.6

Farber *et al.* (1950) and Koss and Durfee (1961) report similar findings and offer the explanation that squamous tumours exfoliate more readily than undifferentiated tumours: we have found that in tumours which histologically contain both anaplastic and squamous elements squamous cells almost invariably exfoliate into the sputum while anaplastic cells are obtained in the bronchial aspirate and smear. However, it must also be realized that squamous cells are practically always identifiable in sputum whereas anaplastic cells may be rendered unrecognizable by shrinkage or degeneration, especially if they are of the small oat-cell type (Wandall, 1944): even when undamaged, this type of cell is the most difficult of all to recognize (Farber *et al.*, 1950; Buffmire and McDonald, 1951). The problem of degeneration does not arise with bronchial aspirate and smears which are fixed immediately, but sputum may not reach the laboratory for several hours.

It is of interest that in the peripheral tumours there was histological evidence of increased squamous differentiation (73.1% of cases), and this was reflected in the cytological findings.

Bronchostenosis and Bronchial Occlusion

Buffmire and McDonald (1951) and Farber (1961) state that the most frequent reason for failure in cytodiagnosis

is obstruction of the bronchus either at the site of the tumour or proximal to it.

We have related the incidence of bronchial obstruction to positive and negative cytology (Table VIII). This shows that in our cases bronchial occlusion or stenosis was not a major factor in failure to obtain positive cytodiagnosis. Indeed, we have found that when stenosis or complete occlusion was demonstrated at bronchoscopy, cytodiagnosis was more often positive than negative. There did, however, appear to be a higher proportion of negative results when bronchial block was demonstrated by bronchogram, but it must be remembered that these tumours were the more peripherally located and therefore would give a higher proportion of negative results in any case (see Table VI).

TABLE VIII.—*Effect of Bronchostenosis and Bronchial Occlusion*

	Complete Block at Bronchoscopy	Stenosis at Bronchoscopy	Complete Block in Bronchogram	No Stenosis or Block Demonstrated
Cytodiagnosis positive (149 cases) ..	27	28	12	82
Cytodiagnosis negative (91 cases) ..	9	9	19	54

We have often observed at bronchoscopy and on examination of resected specimens that tumour tissue is present proximal to a bronchial block. There seems to be no reason why ciliary action should not carry malignant cells from this portion of the tumour into the main stream of bronchial secretion.

Causes of False-positive Results

Three instances of false-positive results were encountered during the period of the study:

1. A man aged 51 had been under observation by a chest physician for 10 years with a lesion in the apex of the left lung, thought to be inactive tuberculosis, although *Mycobacterium tuberculosis* was never identified. A fresh solid lesion in the left upper lobe was noted in a routine follow-up film, and the suspicion of bronchogenic carcinoma was aroused. Conventional investigations were negative, but cells strongly suggestive of anaplastic carcinoma (class 4) were seen in the bronchial aspirate. The left upper lobe was resected and the lesion found to be a caseating tuberculous focus. On reviewing the histological and cytological appearances, epithelioid cells with scanty cytoplasm were thought to be the source of the error.

This source of false-positive results was fully discussed by Wandall (1944) and Koss and Richardson (1955).

2. A man aged 67 was admitted to hospital acutely ill with extensive pneumonia in the right lung. A large abscess formed and he was transferred to the thoracic surgical unit. His general condition improved on treatment with antibiotics and blood transfusion, but the abscess cavity persisted. Bronchoscopy showed inflammatory changes only, but cells strongly suggestive of squamous carcinoma (class 4) were seen in three samples of sputum. Pneumonectomy was performed and the lesion proved to be a chronic pyogenic abscess. Sections of the proximal bronchus showed marked squamous metaplasia.

Squamous metaplasia has been found by numerous authors to be the most common source of false-positive results (Wandall, 1944; Jennings and Shaw, 1953; Koss and Richardson, 1955; Umiker, 1957).

3. A man aged 52 developed sudden pain in the left chest and was admitted to hospital with a provisional diagnosis of coronary thrombosis. Chest radiographs showed a large effusion in the left pleural cavity and a large mediastinal mass.

Aspiration yielded heavily blood-stained fluid. Bronchoscopy showed a slight narrowing of the left lower lobe bronchus, and on bronchography there appeared to be a block in the apico-posterior segmental bronchus. Squamous carcinoma cells (class 5) were identified in the bronchial aspirate. The patient was discharged home with a diagnosis of inoperable carcinoma. When seen again one month later his general condition had amazingly improved and the left pleural effusion had completely cleared. The mediastinal mass was more sharply defined. An aortogram demonstrated a saccular aneurysm of the aortic arch. On reviewing the cytological findings it was found that the specimens examined had been taken from another patient who was bronchoscoped at the same session. The error was purely clerical, due to alteration of identification numbers.

This case illustrates the extreme care necessary in labelling the large number of exactly similar specimens, which are often handled by relatively inexperienced staff. The possibility of clerical error has to be kept in mind if the cytological report does not agree with the clinical opinion and a single positive is followed by a series of negative reports (Umiker, 1957; Koss and Durfee, 1961).

On the other hand, in one case, at first thought to be a "false positive," carcinoma was later proved.

A man aged 52 was admitted to hospital complaining of tightness in the chest, dyspnoea, and cough with blood-stained sputum. Radiographs showed an area of consolidation in the anterior segment of the left upper lobe and a small rounded opacity at the right border of the superior mediastinum. Typical squamous carcinoma cells (class 5) were identified in one specimen of sputum, and suspicious cells (class 3) in the bronchial aspirate. Bronchoscopy, bronchography, and scalene-node biopsy showed no evidence of neoplasm. The lesion in the left upper lobe resolved completely and the mediastinal shadow seemed to become smaller. Of five further samples of sputum examined, only two were satisfactory and these contained no abnormal cells. The patient was discharged with a diagnosis of resolving pneumonia, but was kept under observation. Six months later symptoms recurred and radiographs showed a large ill-defined opacity at the right border of the superior mediastinum; the left lung remained clear. Class 4 cells were identified in the sputum. At right thoracotomy a large tumour was found on the medial surface of the upper lobe, involving the mediastinal pleura. Palliative lobectomy was performed, and the lesion proved to be a poorly differentiated squamous carcinoma.

Other authors have had similar experiences (Spriggs, 1957; Koss and Durfee, 1961). They point out that when positive cytodiagnosis seems incompatible with the clinical diagnosis a careful search should be made in the pharynx, paranasal sinuses, and upper oesophagus, as carcinoma in these sites may be the source of malignant cells in the sputum.

Discussion

In this series positive cytodiagnosis was obtained in 62% of cases of bronchial carcinoma, a figure which compares with other results reported in routine cytodiagnosis (58%—Farber and Mandel, 1960; 65%—Umiker, 1961). Much better results have been published (88.3%—Herbut, 1953 (cited by Grunze, 1960); 92.5%—Sirtori, 1959 (cited by Grunze, 1960); 80%—Koss and Durfee, 1961).

There are several reasons for this difference; for example, only 26% of our patients provided the three adequate samples of sputum generally considered to be necessary, and in 24% of cases no adequate sample was obtained. It is perhaps not generally realized how difficult it is to obtain genuine sputum—that is, material which contains alveolar histiocytes. Unless the patient is specifically instructed by an interested nurse in the technique of the deep cough, often only saliva and post-nasal secretions are produced. We have found that the best

results are obtained when the patient is given written instructions, and the ward sister is made personally responsible for collecting good samples. Some patients genuinely cannot produce sputum; it has been stated (Bickerman *et al.*, 1958; Umiker *et al.*, 1960; Koss and Durfee, 1961) that this difficulty can be overcome by artificial stimulation of the cough reflex, using a nebulizer containing warm saline with or without propylene glycol, but we have not yet tried this. The sputum must be sent to the laboratory as soon as possible, as degeneration takes place after 8 to 10 hours (Wandall, 1944). If delay is anticipated the specimen jar should contain 50 to 70% alcohol, which acts as a fixative (Koss and Durfee, 1961).

Rigid criteria of cell identification were maintained, as in surgical cases it is more important to avoid false positives than to have a very high pick-up rate. Our rate of false positives (0.6% of the total cases examined, or 1.2% of the proved cases) agrees with the 1 to 2% generally quoted (Wandall, 1944; Woolner and McDonald, 1951; Jennings and Shaw, 1953; Farber, 1961). As Umiker (1957) pointed out, in cytodiagnosis there is an inverse relationship between sensitivity and reliability. In his experience, if all cases of carcinoma are diagnosed cytologically there is a false-positive rate of 9%; if no false-positive reports are made, 41% of the carcinomas are not recognized. It is of interest that our false positives occurred in the earlier part of the study, an experience frequently reported in the literature.

The time spent on each sample was limited, as the cytology was carried out as a purely routine procedure in a busy general laboratory. The slides were screened by one technician and various pathologists, about 10 minutes being spent on each sample. Positive or suspicious slides were checked by the cytologist. It has become apparent (Wandall, 1944, 1958; Putney, 1959) that the best results are obtained when cytology is carried out on a research basis by one experienced observer, who may spend up to 30 minutes on each sample. When the method becomes routine the percentage of positive findings inevitably drops; Putney (1959), for instance, experienced a drop from 85 to 40%.

We have found examination of bronchial aspirate and smears of very definite value. Theoretically one would expect this, as by these means material for cytology can be obtained from practically every patient whether or not he can produce sputum. In 15% of our cases aspirate or smears contained malignant cells which had not exfoliated into the sputum. Pinniger (1953) has pointed out that about 30% of bronchial cancers do not readily exfoliate; in such cases cells will often be dislodged by the trauma of bronchoscopy and swabbing, and may then be detected in the aspirate and smear.

In this connexion we have found that sputum produced on the day after bronchoscopy frequently contains malignant cells, and on occasion this specimen gives the only positive result. However, it must be remembered that cells damaged by bronchoscopy may assume bizarre forms simulating malignancy (Jennings and Shaw, 1953; Phillips, 1954).

We have found it essential to have a technician present at bronchoscopy sessions, so that the slides are properly and rapidly prepared, and fixed before drying can occur. The swab used for taking direct bronchial smears must be moistened with saline. It is to be emphasized that, in scanty specimens, drying makes malignant cells unrecognizable within seconds.

From the results obtained we are of the opinion that cytodiagnosis is a reliable method, and that the results fully

justify the time and effort expended. In the thoracic surgical unit confidence in the method has steadily increased as experience has been gained, and it is now completely accepted. Except for bronchial biopsy, which is positive in only a fifth of the cases, it is the only method which provides microscopical proof of malignancy in operable tumours. All other methods of investigation provide only presumptive evidence, which may on occasion be misleading. Even at thoracotomy one cannot always be certain that the lesion is a carcinoma. Some clinicians take the attitude that a suspicious lesion will always be resected, but it must be remembered that many of the patients submitted to the thoracic surgeon are elderly, and suffer from impaired cardio-respiratory function. In such patients lung resection, particularly pneumonectomy, carries a high mortality and morbidity, and cannot be lightly undertaken. It is obviously better to operate on a certain diagnosis rather than a probability, and cytodiagnosis doubles the rate of microscopical proof. Even when operative treatment is not possible, microscopical proof of malignancy is desirable for planning radiotherapy, and gives a sound basis for prognosis.

Improvement in our results is obviously possible and can be effected mainly by better organization. By closer co-operation between the clinical and laboratory staffs better specimens can be obtained for examination. A special effort should be made in cases of peripheral carcinoma, which remain the most difficult to prove. In doubtful cases it is justifiable to examine a large number of specimens. A small percentage of false-positive findings (less than 1%) would seem to be inevitable, however great the care taken; but here again close co-operation between clinician and cytologist can reduce these to an absolute minimum. Resolving pneumonia, bronchiectasis, lung abscess, and tuberculosis are the conditions most likely to give rise to false-positive reports (Koss and Richardson, 1955; Umiker, 1957; Farber *et al.*, 1957), and if the cytologist has been informed that such a condition is present he is then on his guard when interpreting cells of "border-line" nature. Dubious cases should always be discussed.

In the laboratory adequate staffing is essential, as over-work results in reduced sensitivity. Pains-taking care must be employed in selecting suitable portions of sputum for smearing (Wandall, 1944; Phillips, 1954; Umiker, 1957), and malignant cells can easily be missed if screening is done too quickly by a tired observer (Pinniger, 1953). No one should be expected to screen for more than four hours a day, as after this time concentration is impaired and errors of judgment tend to occur with increasing frequency. In our laboratory this corresponds to 30 slides. Ideally, screening should be done by specially trained technicians and suspicious or positive cells discussed with the cytologist, who is then not overburdened by the routine work. We have found that technicians with an aptitude for the work can be trained to screen in three months, though it takes longer to achieve confidence. The time expended on each specimen (10 minutes) is roughly equivalent to that required to screen for acid-fast bacilli, and under present conditions the search for malignant cells is apt to be a good deal more rewarding. We believe that an efficient cytological service is within the resources of a general pathological laboratory.

Summary

Exfoliative cytology was employed as a routine procedure in the investigation of 240 cases of bronchial

carcinoma admitted to a surgical unit. Positive results were obtained in 62% of these cases, as compared with 31% positive results from bronchial biopsy. When cytology was added to the older-established diagnostic methods the number of cases in which the surgeon was left in serious doubt about the diagnosis was reduced from 20% to 9%.

Material for examination was obtained from sputum, bronchial aspirate, and bronchial smears. Each method considered individually yielded approximately 40% of positive results.

Although a higher proportion of positive results was obtained in advanced cases, cytodiagnosis was positive in 49% of operable cases. False-positive reports were made in three cases.

The percentage of positive results was influenced by the position of the tumour in the lung and by the histological type of the tumour.

It was concluded that cytodiagnosis is a reliable and useful method in the diagnosis of bronchial carcinoma. Means of improving results were discussed.

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