Diagnosis of Cancer of the Lung by the Cytologic Method*

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The application of the fixation and staining technique developed by one of us (Papanicolaou)1,2 in the study of sputum for cancer cells was first used by us June 22, 1945. The material was procured from a patient whose symptoms were those of a man who was discharged from the United States Navy in April 1945 as a psychoneurotic. His routine chest plate was reported as negative. He had a chronic, so-called "tobacco" cough, anorexia, insomnia, restlessness, nervousness and weight loss. On June 5th, 1945 he coughed up a small quantity of blood and a chest x-ray examination revealed an infiltrative lesion in the right upper lobe with nodes along the right mediastinal border. Bronchoscopy and bronchial washings were negative. Sputum smears showed typical cancer cells. Subsequent exploratory operation revealed an inoperable bronchogenic carcinoma (Figures 1, 2 and 3).

Since the above date, over 1,300 cases have been studied. The specimens were procured primarily from patients of the New York Hospital and the Memorial Hospital. A monograph is now under preparation in which a description of the cytologic findings and a statistical analysis of the diagnostic accuracy of this method will be given. In a tabulation of 298 cases already reported in the American Journal of Public Health,3 the accuracy was approximately 95 per cent for the positive reports (Classes IV and V)† and 85 per cent for the negative (Classes I and II). Of the cases reported as suspicious (Class III), approximately 50 per cent proved subsequently to be positive.

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†Smear reports have been given on the basis of the following classification:

Negative.
Class I. Absence of atypical or abnormal cells.
Class II. Atypical cells present but without abnormal features.
Suspicious.
Class III. Cells with abnormal features suggestive but not conclusive for malignancy.
Class IV. Cells and cell clusters fairly conclusive for malignancy.
Class V. Cells and cell clusters conclusive for malignancy.

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The technique of preparing and staining smears from sputum may be summarized as follows:

Sputum is expectorated directly for examination or put immediately into 70 per cent alcohol, in order to secure a good fixation and preservation of the cells. It is then spread on slides which have been previously coated with a thin film of Mayer's albumen. The smears are immersed, while moist, in equal parts of 95 per cent alcohol and ether, for at least thirty minutes. They are then stained in hematoxylin, OG6 and EA65, following procedure No. 267.14

Aspirated bronchial secretions and bronchial washings are mixed immediately with an equal volume of 95 per cent alcohol and ether.
and centrifuged for thirty minutes at medium speed. Smears are made from the sediment, fixed promptly in equal parts of 95 per cent alcohol and ether and stained by the same method as the sputum smears.

During the early phase of the work, most of our examinations were limited to a single sputum specimen. Repeat sputum specimens and aspirated bronchial secretions or washings were made available to us in a relatively small number of cases. We now request repeat specimens as well as aspirated bronchial secretions or washings in all cases in which smear findings have been negative or suspicious. In some instances, more particularly in the early cases the number of exfoliated cancer cells may be small and the chance of missing a positive case greater if only one specimen of either type is examined.

The clinical value of the cytologic method is demonstrated by the fact that in many instances of pulmonary neoplasm, it furnished the primary diagnosis or the only preoperative histologic positive evidence. Over twelve pneumonectomies have been performed at the Memorial Hospital and the New York Hospital with a Class V smear report as the only positive preoperative histologic evidence to justify surgery.

The diagnostic value of the cytologic method is exemplified by the following two cases:

Case 1: D. W., L959, Male, 50 years old.


Physical Examination: (1) Moist rales, right posterior lateral base.
(2) Old right apical tuberculosis.

Figure 4a and 4b, Case L959: Photographs of x-ray plates showing infiltrative process in base of right lung.
X-ray Report: Infiltration in right lower lung fields. Findings seem most consistent with an inflammatory process (Figure 4).

Bronchoscopy: Entirely negative.

Bronchial Washing Smear (Figure 5) reported as follows: “Conclusive evidence of a malignant neoplasm. Malignant cells are numerous. Class V.”

Pneumonectomy was performed. After the operation the smear became negative.

Gross Specimen: Basal portion of lower lobe is almost completely replaced by large, moderately firm tumor mass.

Section of lung (Figure 6): Carcinoma of lung Grade II. Peripheral broncholar type, having papillary and pseudoglandular features.

Case 2: W. M., L593, Male, 56 years old.

Symptoms: (1) Chest pain for 8 months. (2) Chronic cough. (3) Sputum, profuse. (4) Weight loss of 14 pounds.

Physical Examination: Suppressed breath and voice sounds in right lower chest.

X-ray (Figure 7): “An endobronchial tumor as well as bronchiectasis must be considered.”

Bronchoscopy: Entirely negative.

Bronchial Washings (Figure 8): “Conclusive evidence of a malignant neoplasm, most likely a bronchogenic carcinoma. Class IV-V.”

Pneumonectomy was performed.

Gross Specimen: Infiltrating tumor mass is seen at the bifurcation of the right lower lobe bronchus.

Section (Figure 9): Bronchogenic epidermoid carcinoma Grade III.

The extrapulmonary nodes show no tumor.

Diagnosis by the cytologic method is based on the identification of malignant cells which may appear either singly or in clusters. Small fragments of tissue in the form of cell clusters are found frequently in cancer smears. The criteria are, therefore, cytologic as well as histologic. Of the cytologic criteria, the most patho-
nomonic are those related to changes in the size, form and consistency of the nucleus. In certain types of carcinomas, as the epidermoid, cancer cells display striking structural abnormalities, which greatly facilitate their detection. Of the histologic criteria, the most significant are the irregularity in pattern, the anisocytosis and anisocaryosis and the crowding of the cells within each group.

In infectious processes, such as pulmonary tuberculosis and pneumonia, exfoliated cells may show atypical features but these are in no way, comparable to those found in carcinoma cells. One condition in which exfoliated cells may appear in clusters
suggestive of a neoplastic type of exfoliation is bronchiectasis. Because of such cell groups, false Class IV positive reports have been given in the first three cases of this type. We now feel that the atypical cells found in bronchiectasis can be differentiated from true malignant cells by the absence of nuclear abnormalities and by some distinctive structural characteristics. Oat cell carcinomas present a greater difficulty in diagnosis because of the smallness of the cells which may be easily overlooked unless found in sizable groups. Epithelial pearls when found in a sputum or an aspirated bronchial secretion always raise strong suspicion of a malignant neoplasm. Dense groups of lymphocytes are also highly suggestive. Thus far, we have noted such groups only in a small number of positive cases.

In the past three years, we have come to believe that the cytologic method is of definite value as an aid in diagnosing cancer of the lung. Evaluation of the advantages of this method to the clinician may be summarized as follows:

It helps in the diagnosis of obscure cases. In some instances where bronchoscopy and aspiration biopsy were negative and the x-ray examination inconclusive, a positive sputum report revealed the true nature of the lesion.

It aids in the earlier diagnosis of pulmonary neoplasm. At times, the sputum report has been positive from a day to weeks before any other histologic evidence of cancer was obtained. It is, therefore, of value for screening purposes in cancer detection clinics.

It tends to accelerate the diagnosis and to increase the percentage of operable cases. This is of particular importance since it enhances the chance of cure of these patients through surgical intervention. The poor results with x-ray therapy are only too well recognized. The gratifying results of early surgery are generally well appreciated.

It is particularly useful in establishing a diagnosis of carcinomas of the superior sulcus, so-called Pancoast's tumors. Tumors in this part of the lung are inaccessible to the bronchoscope. When x-ray findings are meagre, bronchial washings from both right and left main bronchi may decide the issue. Recently we had such a case in which the washing from the right main bronchus was positive (Class V) whereas the reading from the left was negative (Class I).

Because of its technical simplicity and low cost, repeated specimens can be obtained. This makes it particularly advantageous in postoperative and postirradiation follow-up.

CONCLUSION

We wish to emphasize the difficulty in interpreting smears and the need of adequate training for laboratory men who wish to
undertake this type of work. The value of the method depends largely on the training and proficiency of the person interpreting the smears.

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Deseamos recalcar la dificultad de interpretar los frotes y la necesidad del entrenamiento adecuado de los médicos de laboratorio que desean llevar a cabo esta clase de trabajo. El valor del método depende en gran parte del entrenamiento y la habilidad de la persona que interprete los frotes.

REFERENCES


Discussion

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This is an important and timely subject, because carcinoma of the bronchus is unquestionably on the increase. Whether this is real or apparent is beside the point; there are more patients with carcinoma. Surgeons are treating it satisfactorily but the difficulty lies in getting patients to them early so that extirpation of carcinoma still can be done. Our attention was directed forcibly to this several years ago, when Dr. Herbut and I checked the cases of carcinoma of the bronchus that we had diagnosed by bronchoscopic biopsy and then checked to see how many the surgeon was able to treat. This number was small. Obviously there is something wrong. We felt that with the high percentage of positive bronchoscopic biopsies (reports in medical literature vary from 60 to 85 per cent), there should have been more for surgical treatment. The difficulty lay in the fact that a majority of patients are diagnosed too late and a positive bronchoscopic biopsy merely meant that the carcinoma was in a larger bronchus. We therefore concluded that something more should be done to aid in diagnosis particularly in those lesions which could not be visualized bronchoscopically, namely, upper lobe lesions and lesions