Specific Epithelial Degeneration (Ciliocytophthoria)
in Inflammatory and Malignant Respiratory Disease*

MILTON B. ROSENBLATT, M.D., F.C.C.P.,** SALVADOR TRINIDAD, M.D.,***
JAMES R. LISA, M.D.† AND VICTOR TCHERTKOFF, M.D.‡
New York, New York

INTRODUCTION

Diagnostic cytology in pulmonary disease has been concerned chiefly with the recognition of exfoliated malignant cells in sputum and bronchial aspirates. During the past few years, interest has been aroused in a cytologic pattern reflecting degenerative changes in bronchial epithelium in association with certain pulmonary diseases. Papanicolaou designated the phenomenon ciliocytophthoria because of the mass destruction of the ciliated cells. He noted the frequent occurrence of CCP (ciliocytophthoria) in acute pulmonary infections of viral origin and a significantly higher incidence of CCP in patients with lung cancer than in those with chronic inflammatory disease.

Hilding, studying the pathology of the common cold, noted that in profuse clear nasal secretions, there was an abundance of ciliated epithelium some of which had assumed bizarre shapes. Many years later, Bryan and Bryan, using the Papanicolaou staining technique, further defined the morphologic changes in nasal epithelium in upper respiratory infection. They described structural changes consisting of aggregation or margination of the nuclear chromatin, pyknosis of the nuclear material with halo formation, breaking off of cytoplasmic ciliated tufts, and the presence of pink globular bodies in both the nuclear and cytoplasmic portions of the epithelial cell. The occurrence of the pink inclusion bodies assumed particular significance in relation to viral etiology. Hers noted cytologic changes in the sputum of cases of human influenza and described specific degenerative changes comparable to ciliocytophthoria. The effects of influenza virus on ciliated bronchial epithelium of mice were studied by Harford et al. in tissue sections. Inclusion bodies were found in the epithelial cytoplasm of the virus-infected animals, but did not occur in lungs subjected to nonviral irritation or in the normal controls. Pigarevski experimentally induced influenza in mice and demonstrated in ciliated bronchial epithelium the presence of acidophilic inclusion bodies which he believed contained influenza virus. He postulated that the inclusion bodies represented a cellular defense mechanism for extrusion of the infecting agent.

In a series of serologically documented adenovirus and type A viral influenza infections, Knox and Pierce found a striking correlation between these infections and the presence of ciliocytophthoria in the sputum. With the Papanicolaou stain, the acidophilic inclusion bodies were easily identified by the orange-pink color. This report confirmed a previous investigation by Pierce and Hirsch which demonstrated a high incidence of ciliocytophthoria in viral infections diagnosed clinically and/or serologically and, a negligible occurrence, in bacterial pneumonias and other diseases of non-viral origin.
Although Papanicolaou noted 38 morphologic varieties of ciliated columnar epithelial degeneration (Fig. 1, normal epithelium), the abnormalities encountered may be classified into three major changes.

1. **Pyknosis**—condensation of the nuclear chromatin network forming a compact deeply stained mass (Fig. 2).

2. **Clumping**—a redistribution of the nuclear chromatin material into a cluster of small masses, or into a circumferential pattern arranged within the nuclear membrane (Fig. 3).

3. **Tufts**—cellular remnants consisting of cilia and the proximal anucleated cytoplasm formed as a result of a pinching off process (Fig. 4).

Degeneration of the ciliated epithelial cells often produces grotesque, but recognizable, forms. The columnar structure may change to ovoid, or round, as the cell shrinks. On occasion, the cell may elongate and become thin. The cilia may be displaced from their proximal position and emerge from sides of the cell or they may contract into a short stubble. Changes in normal staining affinity may be pronounced, usually, in proportion to cellular disintegration.

The three major types of epithelial degeneration are readily identified, but the numerous gradations of change suggest that tufts, clumping, and pyknosis merely represent progressive stages in the disintegration of the ciliated epithelium and may have no specific intrinsic significance. In serial cytologic studies of nasal secretions in patients with upper respiratory infection, the sequence of events appeared to be aggregation of the chromatin, pyknosis of the nucleus, contraction of the entire cell followed by elongation and pinching off of the anucleated end with the ciliated tuft. It is reasonable to assume that a similar process occurs in the degeneration of bronchial ciliated epithelium.

Inclusion bodies are found in both the cytoplasm and the nucleus. They vary in size and number and are easily recognized by their distribution and affinity for the acidophilic stain which gives them an orange or pink color. The significance of these inclusions and their relation to viral infection requires further clarification. A circumstantial relationship has been established by the finding of inclusions in degenerating nasal ciliated epithelium from patients with the common cold and by their presence in tissue sections of bron-
chial mucosa in mice infected with influenza virus. Nuclear and cytoplasmic inclusions are found in a variety of viral diseases, but their presence, per se, is not proof of viral etiology. Inclusions have not been found in many established viral diseases.

FIGURE 2A: (upper) CCP cell showing marked nuclear pyknosis. The cytoplasm has retracted to an ovoid form and contains many round acidophilic inclusion bodies of various sizes. Cilia have degenerated. Figure 2B: (center) CCP cell showing disintegration and vacuolization of cytoplasm which contains a few acidophilic inclusion bodies. The nucleus has contracted into a small round mass at one end of the cell. Figure 2C: (lower) CCP cell which has retained its columnar appearance. The nucleus shows pyknosis and there are small and large acidophilic inclusion bodies in the cytoplasm. Cilia and cytoplasmic appendage have degenerated.

FIGURE 3A: (upper) CCP cell showing marked irregular clumping and rearrangement of the nuclear chromatin. Acidophilic inclusion bodies are present. Figure 3B: (center) CCP cell showing clumping of the nucleus in a circumferential pattern within the nuclear membrane. The cytoplasm shows vacuolization and a few acidophilic inclusion bodies. Figure 3C: (lower) CCP cell showing elongation, irregular clumping of the nucleus and several large round acidophilic inclusion bodies.

MATERIALS AND METHODS

The subject was given a 2 ounce, screw capped, wide-mouthed glass jar containing 1 ounce of 50 per cent ethyl alcohol. He was instructed in the technique of producing a deep cough and was requested to
extracted from the specimen bottle with forceps, placed in the center of the slide, and crushed with a spreader using a gentle, circular motion. When the material was sufficiently separated, it was spread into a thin, even film and the slide immediately immersed in a screw-top Coplin jar filled with 95 per cent ethyl alcohol and fixed for one hour. Dry or “hard” sputum specimens which tended to wash off in the fixative were protected with a coating of Diaphane which was later dissolved before staining.

The staining procedure utilized the Papa-nicolaou technique7 modified to intensify the acidophilic reaction of cilia and inclusion bodies. The slides were gently placed in a rack and successively run through descending concentrations of alcohol and in distilled water, until hydration was complete. The slide rack was then immered in Harris hematoxylin for ½ minute, rinsed in distilled water, 50 per cent alcohol, and placed for one minute in a solution of 1.5 per cent ammonium hydroxide in 70 per cent alcohol. The ammonium hydroxide was then rinsed out in successively increasing concentrations of alcohol and the rack placed in OG-6 stain for 1¼ minutes. The excess stain was removed by rinsing avoid contaminating the specimen with nasopharyngeal secretions, tissue, etc. The bottles were collected the following morning and the specimens processed within 24 to 48 hours. Delays in processing of more than three days usually resulted in technical difficulties when smearing the slides and often made proper evaluation impractical. Three smears were prepared from each sputum specimen.

Each slide was cleaned in 70 per cent alcohol, wiped dry, and a drop of albumin placed on the surface and spread into a thin film. A small amount of sputum was
in separate dishes of 95 per cent alcohol and the rack immersed in EA-65 for three minutes. The excess stain was similarly rinsed out and the slides were dehydrated in absolute alcohol and cleared in an alcohol-xylol mixture and finally in xylol. The slides were then mounted with Permount and allowed to dry before examination.

Screening

The routine of examination consisted of preparing three slides from each specimen and screening two of the slides under oil immersion lens. Each slide was screened for 20 minutes by a different examiner and the total result recorded. The cases were classified as "positive" or "negative" for CCP on the basis of the presence of at least a total of ten CCP cells on both slides. For practical purposes, a third category, "doubtful" was used temporarily for cases with only a few CCP cells and the slides were later re-evaluated. To facilitate the screening process, only slides containing carbon-laden histiocytes were examined for CCP on the assumption that the presence of these histiocytes was presumptive evidence that the specimen was produced by a deep cough. In order to minimize the tabulation of "doubtful" cases, the presence of nuclear and/or cytoplasmic inclusion bodies was mandatory for a "positive" classification. With the Papanicolaou technique, the differentiation of inclusion bodies from erythrocytes engulfed by histiocytes, eosinophilic granules, or cytoplasmic fragments offered no practical problems.

Results

There were 376 consecutive sputum specimens prepared and screened during the period, November 1, 1961 through June 15, 1962 with the following hospitals participating in the study: Metropolitan, Doctors, St. Francis, Grand Central, Walson, and Fort Jay. The objective was to evaluate the relationship of ciliocytophthora to various respiratory conditions of bacterial, viral, and malignant origin. Equal distribution of specimens from each disease category could not be obtained because of the limitations imposed by the types of cases admitted for hospitalization. Technical difficulties in the examination of the sputum and/or incomplete diagnostic data made it advisable to exclude 75 of the specimens, leaving a total of 301 well documented cases with satisfactorily prepared slides.

Accuracy of diagnosis was assured in the tuberculosis group by including only patients with bacteriologic confirmation either by direct smear or culture. Cases with coexisting pulmonary diseases were excluded. Among the malignancy patients the diagnostic requisite was pathologic examination of tissue obtained at biopsy, surgery, or necropsy. The diagnosis of bacterial pneumonia was accepted when, in addition to radiologic findings, there were positive sputum and/or blood cultures. In the remaining categories, particularly in the viral groups, the diagnostic criteria were, of necessity, based on clinical considerations. These included history, physical examination, clinical course, roentgen findings, compatible laboratory data, and exclusion of other disease entities.

<table>
<thead>
<tr>
<th>Pulmonary Disease</th>
<th>Number of CCP Positive</th>
<th>Per cent CCP Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pulmonary Tuberculosis</td>
<td>62</td>
<td>9.7</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>10</td>
<td>10.0</td>
</tr>
<tr>
<td>Chronic Lung Abscess</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Chronic Bronchitis and Emphysema</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Allergic Bronchial Asthma</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Bacterial Pneumonia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Upper Respiratory Infection (viral)</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>Viral Pneumonia</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>Metastatic Lung Cancer</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Bronchogenic Carcinoma</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td>Acute Bronchitis (viral)</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>301</td>
<td>77</td>
</tr>
</tbody>
</table>

Table 1—Incidence of Ciliocytophthora in Pulmonary Disease
The relation of ciliocytophthoria to the various pulmonary diseases is listed in Table 1. Of the 62 cases of chronic pulmonary tuberculosis, there were six (9.7 per cent) positive for CCP. There were ten bronchiectasis cases with one (10 per cent) positive. The chronic lung abscess group of four had no positives. Of the 28 cases with chronic bronchitis and emphysema, there were two (8 per cent) positive. The six cases with congestive heart failure and the four with allergic bronchial asthma were negative. There were 24 instances of pneumococcal pneumonia and two of staphylococcal pneumonia. For both groups combined, the CCP incidence was three (11.5 per cent). The 41 viral pneumonia cases had 11 (26.8 per cent) positives. Of the 52 instances of uncomplicated upper respiratory infection, there were 13 (25 per cent) CCP positive and 16 cases with acute bronchitis had 12 (75 per cent) positive. The 44 primary lung cancer cases had 25 (57 per cent) positive and the eight secondary lung cancer cases had four (50 per cent).

There were 77 instances (25.5 per cent) of ciliocytophthoria in the 301 cases studied. The positive CCP cases were grouped according to etiologic origin as shown in Table 2. Twelve (15.6 per cent) of the total positives occurred in cases with bacterial infection. This group included tuberculosis, bronchiectasis, chronic bronchitis, bacterial pneumonia and chronic lung abscess. There were 36 (46.8 per cent) CCP positives in the group of diseases of assumed viral origin, namely, viral pneumonia, upper respiratory infection, and acute bronchitis. Group III, comprised of primary and secondary lung cancer cases, had 29 (37.6 per cent) of the total positives.

**DISCUSSION**

The high incidence of ciliocytophthoria in acute viral diseases of the respiratory tract and in bronchogenic carcinoma confirms the findings of previous investigators. In our series, 65 (84 per cent) of the 77 positive CCP cases were either of viral or malignant origin. The relationship of CCP to both conditions presents interesting possibilities. While it is intriguing to speculate that the presence of CCP cells in viral disease and malignancy suggests an etiologic association, pathologic observations indicate that the production of CCP cells in both these diseases may represent an epitheliotropic effect.

Extensive desquamation of columnar ciliated epithelium usually occurs in acute viral diseases of the respiratory tract. This produces large numbers of degenerating epithelial cells in the sputum, many of which can be recognized as CCP forms. In bronchogenic carcinoma, a similar desquamation process may occur due to an entirely different pathogenesis. One of the commonest forms of spread of epidermoid carcinoma is along mucosal pathways. As the malignant tissue expands peripherally along the bronchial tract, its rate of growth is far more rapid than the adjacent uninvolved epithelium (Fig. 5). This deprives the columnar epithelium of necessary nutrient for survival and results in the desquamation of the ciliated cells and subsequent degeneration into CCP forms. A similar phenomenon has been noted in metastatic cancer of the lung following lymphatic invasion, surface penetration, and subsequent mucosal spread.

**Table 2—Etiologic Distribution of 77 Positive CCP Cases**

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Bacterial Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic Pulmonary</td>
<td>6</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Bronchitis</td>
<td></td>
</tr>
<tr>
<td>and Emphysema</td>
<td>2</td>
</tr>
<tr>
<td>Bacterial Pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Chronic Lung Abscess</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12 (15.6%)</td>
</tr>
<tr>
<td><strong>II. Viral Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>13</td>
</tr>
<tr>
<td>Viral Pneumonia</td>
<td>11</td>
</tr>
<tr>
<td>Acute Bronchitis</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>36 (46.8%)</td>
</tr>
<tr>
<td><strong>III. Malignant Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Bronchogenic Carcinoma</td>
<td>25</td>
</tr>
<tr>
<td>Metastatic Lung Cancer</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>29 (37.6%)</td>
</tr>
</tbody>
</table>
The diagnostic and possibly etiologic significance of CCP cells in bronchogenic carcinoma has been referred to by Papanicolaou. In cases suspected of lung cancer, CCP may be present in the sputum for weeks, or months, before cytologic confirmation is possible by the finding of malignant cells. The repeated occurrence of CCP in the sputum is evidence of an epitheliotropic process in the respiratory tract. In patients of the appropriate age group, persistent efforts should be made to investigate for malignant neoplasm.

**Summary**

1. Ciliocytophtoria is a specific form of degeneration of columnar ciliated epithelium of the respiratory tract.

2. Using the Papanicolaou staining technique for the examination of sputum, CCP cells are easily recognized by the formation of tufts, pyknotic and clumped nuclei, and by the presence of acidophilic inclusion bodies in the cytoplasm and nucleus.

3. A study of 301 cases with varied respiratory diseases showed the highest incidence of CCP to occur in patients with acute viral infections and bronchogenic carcinoma.

4. Among 77 cases positive for CCP, 65 (84 per cent) occurred in patients with either viral or malignant respiratory disease.

5. The relationship of CCP formation to viral disease and malignancy is explained by an epitheliotropic process occurring in both conditions resulting in the desquamation, and subsequent degeneration, of large numbers of columnar ciliated epithelial cells.

**Acknowledgment:** The authors acknowledge their deep appreciation to the late Dr. George N. Papanicolaou for his encouragement and advice.

The authors also wish to thank the following for their cooperation in the collection of sputum specimens and preparation of case histories: Lieutenant Colonel George B. Hamilton, M. C., Captain Joseph L. Kunz, Captain Francis I. Kittredge and Captain Charles H. Winterling, Washington Hospital, Fort Dix; Dr. Theodore Ehrenreich, St. Francis Hospital; Dr. Raymond Carnes, Grand Central Hospital and Major Dwight Mors, Fort Jay Hospital. Appreciation is also due to Kermuth Gioppa, Linda Skakandy, Kayla Scheer, and Dr. Jerome Burken for their painstaking technical assistance.

**Resumen**

1. La ciliocitoftoria es una forma específica de degeneración del epitelio columnar del árbol respiratorio.

2. Usando la técnica de tinción de Papanicolaou para el examen de esputos se reconocen las celdillas CCP por la formación de ramos, núcleos picnoticos apelotonados y por la presencia de acidófilos de inclusión en el citoplasma y en el núcleo.

3. Un estudio de 301 casos con enfermedades respiratorias diversas mostró la mayor incidencia de CCP en enfermos con infecciones virales y en carcinoma broncogénico.

4. Entre 77 casos positivos por la formación de CCP, 65 (84 por ciento) ocurrieron ya sea enfermedad viral o en malignidad.

5. La relación de la formación de CCP con la enfermedad viral y la neoplasia maligna se explica por un proceso epiteliotrópico que ocurre en las dos afecciones y que produce descomposición y degeneración subsecuente de gran número de celdillas epiteliales ciliadas.

**Resumé**

1. La ciliocytophtorité est une forme spécifique de dégénérescence de l'épithélium cylindrique cilié du tractus respiratoire.

2. Utilisant la technique de coloration de Papanicolaou pour l'examen de l'expectoration, les cellules avec ciliocytophtorité sont aisément reconnues par la formation de touffes, de noyaux pycnotiques en bouquets, et par la présence d'inclusions de corps acidophiles dans le cytoplasme et le noyau.

3. Une étude de 301 cas atteints d'affections respiratoires diverses montra la fréquence très élevée de cellules avec ciliocytophtorie chez les malades atteints d'infections virales aiguës et de cancer bronchique.

4. Sur 77 cas positifs, 65 (84%) survinrent chez des malades atteints d'affections respiratoires virales ou malignes.

5. Le rapport entre les cellules avec ciliocytophtorie et l'affection virale maligne est expliqué par le processus épithéliotropique de ces deux états, provenant de la desquamation et de la dégénérescence conséquente d'un grand nombre de cellules cylindriques ciliées.

**Zusammenfassung**

1. Spezifische epitheliale Degenerationen (Ciliocytophtorie = CCP) bedeutet eine spezielle Form von Entartung von zylindrischem Flimmerepithel des Respirationstraktes.

2. Verwendet man die Färbetechnik nach Papanicolaou zur Sputumuntersuchung, so lassen sich CCP-Zellen leicht erkennen an der Bildung von geknäuelten pyknotischen und verklumpten...
Kernen und an dem Vorhandensein von acido-
philen Einschlußkörperchen im Cytoplasma und
Kern.
3. Eine Untersuchung von 301 Fällen mit ver-
schiedenen respiratorischen Erkrankungen zeigte,
 daß die größte Häufigkeit von CCP bei Patienten
mit akuten Virusinfektionen und Bronchialcar-
zinomen bestand.
4. Unter 77 auf CCP positiven Fällen kamen
65 (84%) bei Patienten vor, die entweder eine
Virusinfektion oder eine bösartige Erkrankung
des Respirationstraktes hatten.
5. Die Beziehung von CCP-Formation zu
Viruserkrankungen und bösartigen Erkrankungen
läßt sich erklären durch einen epitheliotropen
Prozeß, der bei beiden Krankheitszuständen vor-
kommt und zu einer Desquamation und nach-
folgenden Degeneration von einer großen Zahl
von zylindrischen Epithelzellen führt.

REFERENCES
1 PAPANICOLAOU, G. N.: “Degenerative Changes
in Ciliated Cells Exfoliating from the Bron-
chial Epithelium as a Cytologic Criterion in
the Diagnosis of Diseases of the Lung,” New
2 PAPANICOLAOU, G. N., BRIDES, E. L. AND
RAILEY, C.: “Degeneration of the Ciliated
Cells of the Bronchial Epithelium (Ciliocytop-
thoria) in its Relation to Pulmonary Disease,”
3 PAPANICOLAOU, G. N. “Cellular Changes in
the Development of Pulmonary Cancer as Re-
vealed by Cytology: A Case Report,” Acta
Otolaryng., 12:133, 1930.
5 HILDING, A.: “Summary of Some Known Facts
Concerning the Common Cold,” Trans. Am.

RESECTION OF CHRONIC POSTINFARCTION MYOCARDIAL ANEURYSMS

In five patients with chronic postinfarct left ven-
tricular aneurysms, ranging in age from 47 to 63
years, the time lapse between the initial Infarct and
the appearance of the left ventricular aneurysm was
two weeks to two years. The interval between the
initial infarct and surgery was from five months to
six years. Less than adequate bed rest following the
infarct, multiple infarcts, and systemic hypertension
were other possible etiologic factors present in the
above-described group of patients. Right heart
catheterization was performed in two patients and
showed a reduced cardiac output and elevated pulmo-
nary pressure in one, with a return to normal after
corrective surgery. The diagnosis was suggested by
electrocardiographic tracing and chest roentgeno-
grams, supported by kymography and confirmed by
angiography. The method of complete excision with
ventriculoplasty and cardiopulmonary bypass was
used in all our patients and is recommended as the
method of choice.

All patients survived the operation, and followup
from six months to 40 months after operation have
shown no late deaths to date and all have been re-
habillitated.

LILLESHE, C. W., LEVY, M. J., DEWALL, R. A. AND
WADDUEN, H. E.: “Reection of Chronic Post-infarction Myocardial