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Ciliocytophthoria: Relationship to Viral Respiratory Infections of Humans.*† (24084)

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Papanicolaou(1) described abnormal ciliated epithelial cells found in sputum specimens from some patients with acute and chronic pulmonary disease. The phenomenon was designated ciliocytophthoria, abbreviated as "CCP." The possible significance of CCP as a diagnostic aid in infections of the respiratory tract, and its correlation with the presence or later development of lung cancer were suggested.

The present communication reports observations of sputum cytology, with special emphasis on CCP, in patients with various types of respiratory disease. The results show that CCP is commonly found during pulmonary infections of viral etiology.

Methods. Single specimens produced by deep coughing were collected in 70% ethyl alcohol and smeared and stained by Papanicolaou technic(2). From many patients daily samples were obtained during illness and convalescence. The presence or absence of CCP was ascertained using as criteria the degenerative changes of ciliated epithelial cells described and illustrated in the original report (1). Only those specimens produced by a deep cough (as evidenced in the smear by presence of histiocytes containing carbon particles) were included in the analysis. Smears composed predominantly of squamous epithelial cells and devoid of dust cells were discarded as unsatisfactory. The normal cytogram of deep cough sputum specimens has been described and illustrated by Carabelli (3). Our data were obtained from specimens processed within one or 2 days after sample was received in the laboratory. It may be of practical use to mention, however, that CCP can be demonstrated in positive sputum specimens stored in 70% alcohol at 4°C up to 6 months. Although other cell types are not

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TABLE I. Presence of CCP in Sputum.

Illness	Total No. patients	Total No. patients (CCP positive)
Acute respiratory disease		
Viral influenza	30	26
Primary atypical pneumonia	3	3
Unknown etiology, probably viral	12	11
*Idem**	14	14
Bacterial pneumonia	8	1
Chronic respiratory disease		
Sarcoidosis	24	3
Pulmonary tuberculosis	7	1
Bronchitis	3	1
Asthma	3	3
Carcinoma of lung	2	1
Emphysema and fibrosis	1	0
Non-respiratory disease		
Gastrointestinal bleeding	1	0
Pyelonephritis	1	0
Cerebral thrombosis	1	0
Multiple myeloma	1	0
Rheumatic heart disease	1	0
Myocardial infarction	1	0

* Laboratory personnel (non-hospitalized).

well preserved after prolonged storage, nevertheless CCP is readily apparent. In patients suffering from virus influenza (Asian strains of type A), the etiologic diagnosis was established by studies of other investigators. Their data on identification of viral agents(4,5) and clinical observations(5) are published elsewhere.

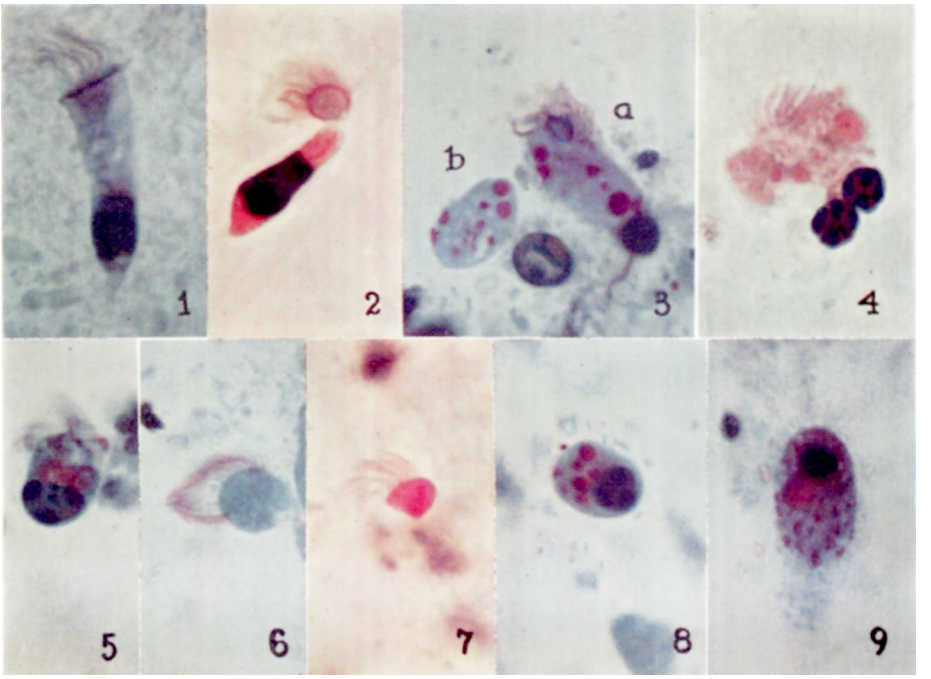
Results. The accompanying photomicrographs illustrate the following abnormal morphological patterns of ciliated epithelial cells observed in CCP positive specimens: nuclear degeneration, pinching off of distal portion of the cell resulting in free ciliated tufts devoid of nuclei, acidophilic inclusions of various sizes and numbers in cytoplasm of the whole intact cell as well as in free ciliated tufts and in remaining basal segments. The acidophilic nature of the inclusion bodies allows them to be easily identified as orange or pink spherical structures within the faint blue or light pink background of cellular cytoplasm.

We emphasize that not all morphological abnormalities described, are found in each positive specimen. The relative proportion of one type to another and its significance in respect to the disease process has yet to be analyzed.

Table I summarizes results of examination for CCP in sputum from patients with various illnesses. It can be seen that CCP was strikingly associated with acute respiratory disease of established or probable viral origin. Specimens from persons infected with influenza virus (Asian strains of type A) showed CCP in 26 of 30 cases. In addition, sputa from the small number of patients presenting the syndrome of primary atypical pneumonia associated with cold hemagglutinins all revealed CCP. Specimens from patients suffering from acute respiratory infection of probable viral origin were positive for CCP almost without exception; in these individuals the clinical pattern of the illness (insidious onset, constitutional symptoms, absence of pneumonic infiltration and of leucocytosis, and recovery without antimicrobial therapy) suggested strongly a viral causation, but all efforts to establish an etiologic diagnosis were without avail. Similarly CCP was present in sputa from non-hospitalized laboratory personnel exhibiting symptoms suggestive of a viral respiratory infection.

In contrast, CCP was found rarely in sputum from patients with bacterial pneumonia, or with various chronic respiratory diseases. Some of the rare CCP positive specimens in these groups were obtained from patients in whom an intercurrent viral infection was suspected. CCP was not observed in sputum from a small number of patients with diseases of other organ systems.

Table II demonstrates the presence of CCP in serial sputum specimens from patients infected with Asian strains of influenza virus (type A), as established either by virus isolation, or by demonstration of rising serum antibodies, and in many instances by both methods. In each of these cases, specimens obtained during the first few days of illness were comprised predominantly of CCP and mononuclear cells. The engulfment of ciliated tufts or basal fragments of CCP by histiocytes was occasionally observed. In those cases which ran an uncomplicated course, CCP persisted during the first week of illness; sputum smears made during subsequent convalescence often showed numerous large, multinucleated histiocytes with orange or pink cytoplasm.



PHOTOMICROGRAPH 1. Magnification × 1100. Morphological Changes Characteristic of Cilio-cytophthoria (CCP).

1. Normal ciliated cell.
2. Pinching off of ciliated portion and nuclear change of basal segment.
3. (a) Pyknotic nucleus and inclusions of various sizes in cytoplasm of intact cell.
   (b) An anuclear segment containing inclusions.
4. Two cells undergoing disintegration. Note degenerative nuclei and large inclusions in cytoplasm.
5. Nuclear change with characteristic chromatin grouping in intact cell.
6 and 7. Free ciliated tufts.
8 and 9. Basal segments containing pyknotic nuclei and cytoplasmic inclusions.

The photomicrographs were taken by Mr. Julian Carlile of The Rockefeller Institute.

TABLE II. Duration of CCP in 13 Patients with Viral Influenza.

Presence of CCP in sputum (days after onset of illness)															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
+	+	+	+	+											
+	+	+	+												
+	+	u.s.	u.s.	+	+										
	+	+													
		+	+	+	+	u.s.									
		+	+	+	+	+	+	+	u.s.				0		
			+	+		u.s.				u.s.					0
			+	+	+										
			+	+	0										
		+		+	+			+							
			+	+	+	+						0			
			+	+	u.s.	0			+			0	+		0
			+	u.s.	0	0			+		0		0		

Blank space on chart indicates specimen not received. (u.s.) indicates unsatisfactory specimen.

Specimens identified in descending order as follows: P.C., L.W., E.T., E.C., M.B., Tuc., V.G., Cou., Mur., Rui., Lah., Ger., Nad.

Of special interest were observations on several influenza patients who developed complicating bacterial pneumonia. The development of bacterial pneumonia coincided with a striking change in cytological pattern of the sputum smear, the cytogram changing from that of CCP and small and large mononuclear cells seen during initial influenza to a picture comprised predominantly of polymorphonuclear leucocytes during the bacterial pneumonia.

Discussion. The present studies were undertaken primarily to gain information about the significance of a particular type of degeneration (ciliocytophthoria) observed in exfoliated ciliated epithelial cells in certain sputum specimens. Is the occurrence of CCP the result of specific damage to the respiratory tract, or do these abnormal cellular changes appear in shed ciliated cells regardless of the factor producing exfoliation? Occasional columnar ciliated cells were often present in specimens from patients with acute bacterial bronchopulmonary disease or various chronic lung conditions, yet the degenerative changes of CCP were not seen in these instances by us or by others(3,6). Thus, it is suggested that there is, indeed, a certain specificity associated with CCP.

On the other hand, CCP was observed in smears of sputum obtained from patients with a variety of acute viral respiratory infections. Further studies are required to determine whether or not the numerous viral agents which infect the tracheobronchial tree differ one from the other in respect to the quantity or type of CCP which they incite.

Previous workers have described abnormal changes in ciliated respiratory epithelium accompanying viral influenza infection and have suggested the usefulness of these observations in establishing a tentative diagnosis(7,8). In addition, Hers(7) has observed similar degenerative changes in ciliated cells in specimens obtained from fatal cases of measles and varicella bronchopneumonia, and has suggested that these alterations are not specific for influenza but represent infection with epitheliotropic viruses in general. The fact that inclusions characteristic of CCP were not described by Hers(7) may be due to the different technics of staining employed. Inclusions in tracheobronchial epithelium obtained at autopsy from cases of varicella pneumonia have been described by others(9,10).

The number of specimens available to us from patients with established pulmonary carcinoma was insufficient to permit evaluation of a possible relationship between CCP and lung neoplasms. For the same reason, the presence of CCP in bronchial asthma cannot be properly assessed. It is possible that the asthmatic attacks in the 3 cases studied may have been provoked by viral infections. CCP has not been described by others who examined bronchial aspirates or sputum specimens from a large series of patients with asthma(3,6).

There is great need at present for an ac-

curate method of making a prompt diagnosis in respiratory infections. Although it is well recognized that a high proportion of acute illnesses accompanied by cough and fever are of viral origin, therefore not requiring the administration of antimicrobial agents, the physician is usually forced to decide on specific treatment before results of bacteriological and virological examinations are available. Therefore, antibiotic therapy in acute respiratory infections is commonly instituted empirically. The results of our investigation suggest that cytological examination of sputum may be helpful in prompt diagnosis of acute pulmonary infections. In addition to the clinical pattern and other laboratory features of illness, the presence or absence of CCP in sputum from a satisfactory deep cough specimen provides a diagnostic aid which may serve to distinguish between infections of viral and bacterial etiology.

Summary. 1) Sputum specimens from patients with acute and chronic pulmonary diseases were examined cytologically by the Papanicolaou technic. Certain abnormalities in exfoliated ciliated epithelial cells (ciliocytophthoria) were observed in specimens from a high proportion of individuals with viral respiratory infections; in contrast, ciliocytophthoria was seen only rarely in sputum preparations from patients with acute or chronic pulmonary disease of non-viral etiology. 2) Sputum cytology may prove valuable for prompt differential diagnosis between viral and bacterial respiratory infections.

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Superior Olive in the Alligator.* (24085)

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Rasmussen(3) described for the cat peduncular fibers which leave the central nervous system between the 2 divisions of vestibular nerve and dorsal to rootlets of the pars intermedia. These fibers then course in the inferior division of the vestibular nerve as far as the ganglion associated with the main saccular ramus to the cochlear nerve. His findings were based on experimental material studied by the Marchi method(4) and by chromatolytic methods. Rasmussen(3) states that it was "extremely difficult, if not impossible, to determine the exact cells of origin of the peduncle by the Marchi method" but that it was "possible to delimit a definite area of origin with the aid of small lesions variously placed. The possibility of peduncular fibers passing through the olive from elsewhere was ruled out by circumscribing it with lesions." After section of the eighth nerve he found, in cresyl violet stained sections, no significant alterations or cell loss in the superior olivary complex proper, but on the contralateral side many retro-olivary cells appeared shrunken.

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