

Ultrastructural Aspect in the Immotile Cilia Syndrome^{*1)}

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ABSTRACT

Since presentation of the concepts of the immotile cilia syndrome, much attention has been paid to function and structure of respiratory cilia, many authors have pointed out that ultrastructural abnormality of cilia was attributed to the immotility of cilia.

We investigated a woman suspected of the immotile cilia syndrome by electron microscopy, cross sections of cilia obtained from respiratory tract showed lack of dynein arms, radial spokes and central sheath, moreover so-called compound cilia.

INTRODUCTION

In 1975 Afzelius²⁾ pointed out that patient with ciliary dysfunction had lack of dynein arm by electron microscopy. In 1977 Eliasson³⁾ and his co-workers presented a more extensive analysis of the defects in ciliary structure and called this disorder, which consisted of recurrent respiratory infection and male infertility as the clinical presentations of ciliary dysfunction, immotile cilia syndrome.

Since Kartagener's triad is obvious clinical expression of abnormal cilia, it has been suggested that Kartagener's syndrome be listed as a subset of a category of the immotile cilia syndrome. In Japan Nagai⁴⁾ and his co-workers reported the first case of the immotile cilia syndrome in 1982.

Since presentation of the concepts of the immotile cilia syndrome, much attention has been paid to function and structure of respiratory cilia. We observed the ultrastructural finding of respiratory cilia, obtained from patient suspected of Kartagener's syndrome by electron-microscopy and diagnosed as the immotile cilia syndrome.

CASE REPORT

A 34 year old female, who began to complain of cough, purulent sputum and fever in the beginning of January '82 consulted to house doctor. She had been followed by medications

for two months with a diagnosis of pneumonitis. In May she was transferred to NATIONAL SANATORIUM HIROSHIMA HOSPITAL because of the increased density on chest film and positive sputum for acid fast bacilli. Since early childhood, she had been suffered from recurrent nasal discharge, cough and purulent sputum and diagnosed as bronchial ectasis and situs inversus. She also had a history to undergo surgical operation for chronic sinusitis at 15 year old.

Physical examination

She was moderately developed and nourished and in no acute distress. No digital clubbing and cyanosis was present. Medium consonating moist rales were heard at the base of both lungs on auscultation. Maximum cardiac impulse was palpable over the right precordium. temperature is 37.8C. Pulse rate 85 per minute. respiratory rate 19 per minute.

Laboratory data (Table 1)

Laboratory data on the patient's initial visit showed reduced pulmonary function and positive sputum for atypical acid fast bacilli.

Chest film

Chest film (Fig. 1) revealed dextrocardia with situs inversus of abdominal viscera with right gastric fundus, left liver shadow. And prominent basilar bronchial marking consistent with the diagnosis of bronchial ectasis.

Bronchoscopy

Patient underwent bronchoscopy with finding

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Table 1. Laboratory data on admission

Hematology	Immunology
RBC $507 \times 10^4/\text{mm}^3$	CRP —
WBC $4700/\text{mm}^3$	RA —
stab 2%	ASLO —
seg 72%	MPHA —
lymph 24%	IgG 1100 mg/dl
mono 1%	IgA 308 mg/dl
eosino 1%	IgM 232 mg/dl
baso 0%	
Biochemistry	Pulmonary function
T, P 7.0 g/dl	V. C 1700 cc
Alb 4.2 g/dl	%V. C 55%
A/G 1.5	FEV 1.0% 50%
ZTT 7.0	Ph 7.45
Tot-chol 178 mg/dl	Pco ² 35 mmHg
BUN 20 mg/dl	Po ² 87 mmHg
GOT 17 u	HCo ³⁻ 25 mmol/L
LDH 349 mU/ml	
Al-p 5.0 K-AU	
Sputum culture	M. intracellulare.

of slight inflammatory change on bronchial mucosa.

Methods

Biopsies of bronchial mucosa were taken from both upper lobe bronchus under local anesthesia, the specimens were immediately fixed in 2.5% glutaraldehyde solution, postfixed in osmium tetroxide and uranyl acetate and examined by the HITACHI H-600 electron microscope.

Ultrastructural finding

Observing the cross sections of cilia under electron microscope, the ciliary membrane was seen almost normal. The structure of doublet microtubules was normal as to position and appearance, however, two sets of dynein arms, which must project from each doublet were found to be defective in almost all microtubules. The radial spokes and central sheath were not clearly distinguished, (Figs. 2 and 3). Moreover, as shown in (Figs. 4 to 7), several 9+2 axonemes (for example, two, three, five and eight axonemes) were found within single cilium.

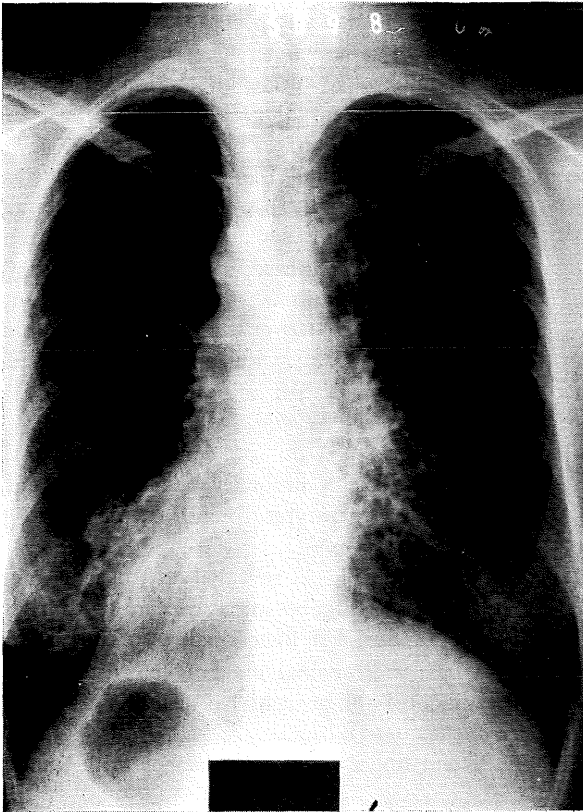


Fig. 1. Chest film showed dextrocardia with situs inversus and bronchial ectasis

DISCUSSION

The case just described is thought to be a classic example of Kartagener's syndrome with chronic sinusitis, situs inversus and bronchial ectasis. Kartagener's syndrome is characterized by lack of mucociliary transport and abnormalities in structure and function of cilia have been described. Recently with the advent of electron microscopy, ciliary abnormalities could be discovered, analyzed and correlated with clinical problem.

Eliasson et al. introduced the term immotile cilia syndrome in 1977, when they discovered that the lack of dynein arm in the cilia had caused the immotilities of cilia themselves and Kartagener's syndrome was regarded as a subset of a category of the immotile cilia syndrome. They strongly emphasized the close relationship between ultrastructural abnormalities and ciliary dysfunction.

The respiratory tract cilia, extending to the level of the respiratory bronchioles, are about 6.0μ in length and 0.24μ in diameter. Each cell has approximately 200 cilia.

Rhythmic beating of the cilia play a very important role as to mucociliary transport. Respiratory cilia clear the airway of inhaled materials and secretions.

The structure of the cilium is complicated as shown in (Fig. 8). The cilium is composed of

a single axoneme surrounded by a ciliary membrane. The axoneme is composed of two central microtubules and peripheral doublet microtubules, peripheral doublet microtubules are designated as the subfiber A and subfiber B. Projection from subfiber A in the direction of subfiber B of the adjacent doublet is structure known as dynein arm, in addition, extending from subfiber A in the direction of the central microtubules is structure known as radial spoke.

Dynein arm is found to be essential in the generation of ciliary sliding motion and the defect in ciliary movement is attributed to the absence of dynein ATP ase^{7,10}, in addition to the absence of dynein arm, other ultrastructural defects have been reported in the immotile cilia syndrome, eg. defect of radial spokes⁴ and defect of central sheath³.

The case we investigated is thought to have complications with defect of these structure, defect of dynein arms and defect of radial spokes. Further characteristic findings are seen, they are so called compound cilia¹ which contain several axonemes in a cilium.

However what is the most fundamental and the most characteristic ultrastructural abnormality in the immotile cilia syndrome is the defect of dynein arm as pointed out by Afzelius and many other authors. And dynein arms were found to have ATP ase which, when hydrolyzed ATP, generate free energy, causing a sliding

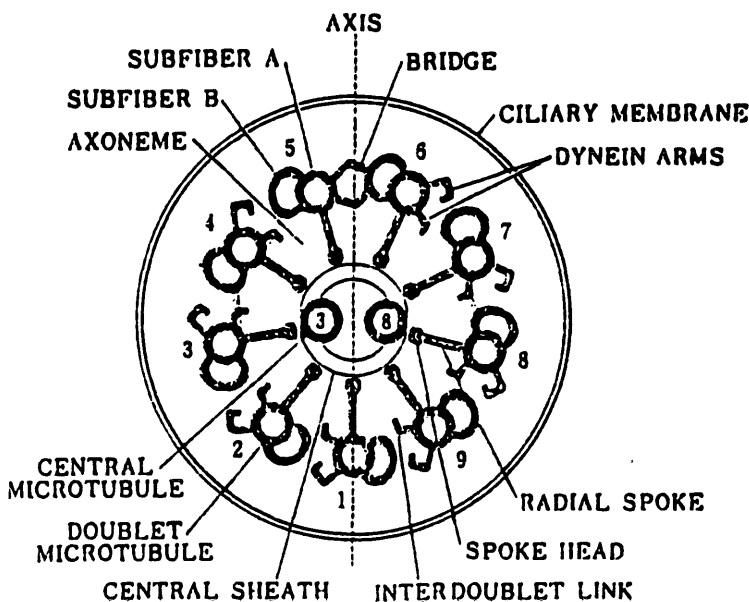


Fig. 8. Terminology of the components of the normal ciliary axoneme.

motion.

Moreover, compound cilia is rare but seen in heavy smoker with bronchial carcinoma, patient with bronchial ectasis and chronic sinusitis.

According to recent investigation by Rossan⁹⁾ et al. (1981), since the cilia with the defect of dynein arms lack coordination but retain some motility, this syndrome is more properly called as ciliary dyskinesia⁶⁾ or dysfunction syndrome.

Undoubtedly new investigations in relation to mucociliary transport from the biochemical and anatomical point of view may not only provide a definitive understanding of the immotile cilia syndrome but also lead to a treatment of this syndrome.

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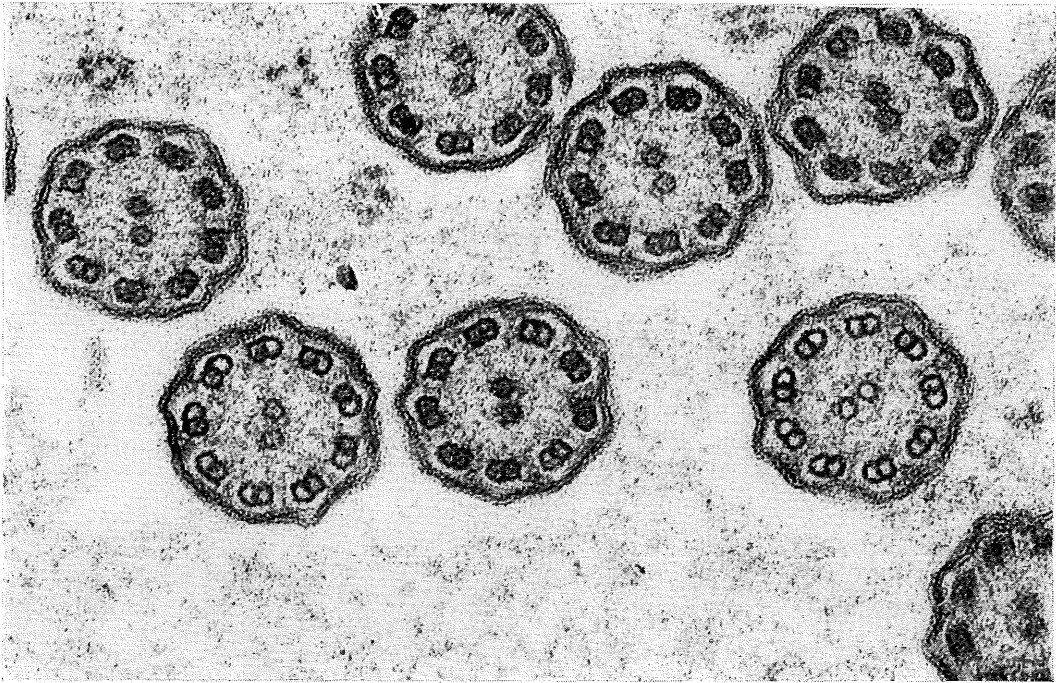


Fig. 2

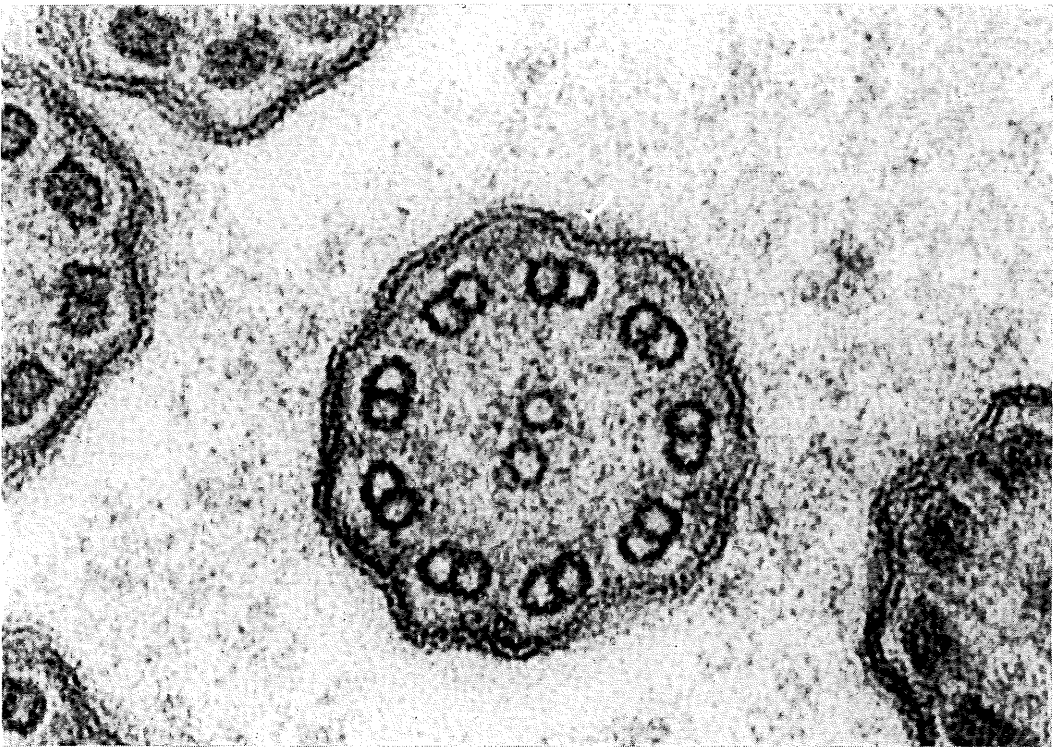


Fig. 3

Figs. 2 and 3. Cross sections of cilia. Dynein arm, radial spoke and central sheath can't be distinguished clearly.

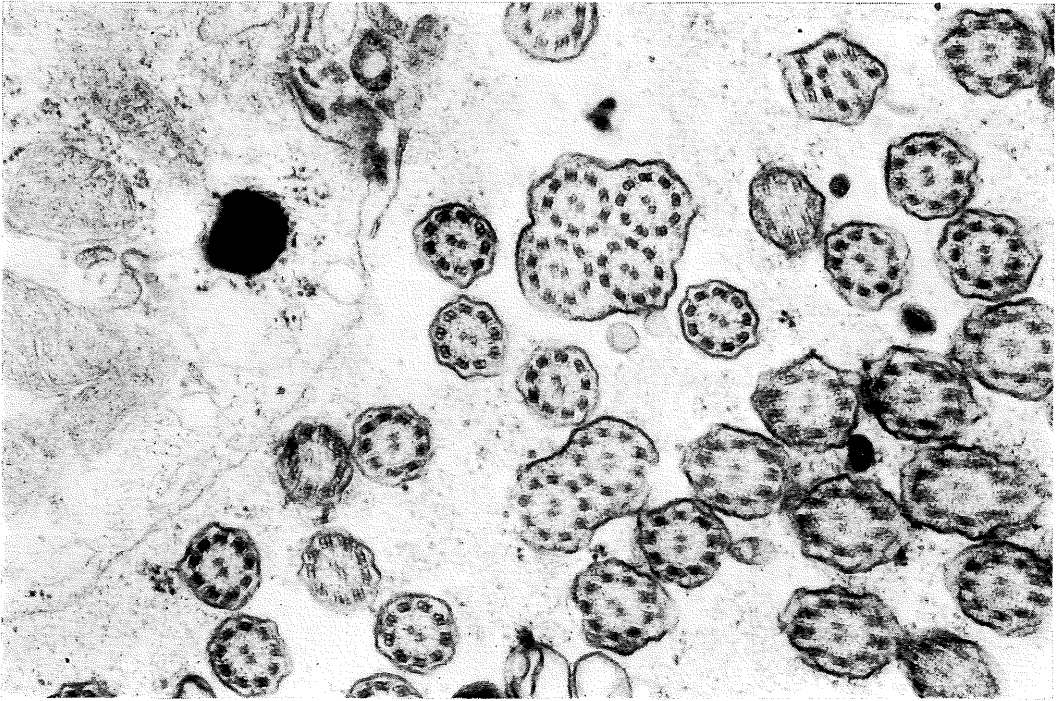


Fig. 4. Two and four 9+2 axonemes in a cilium

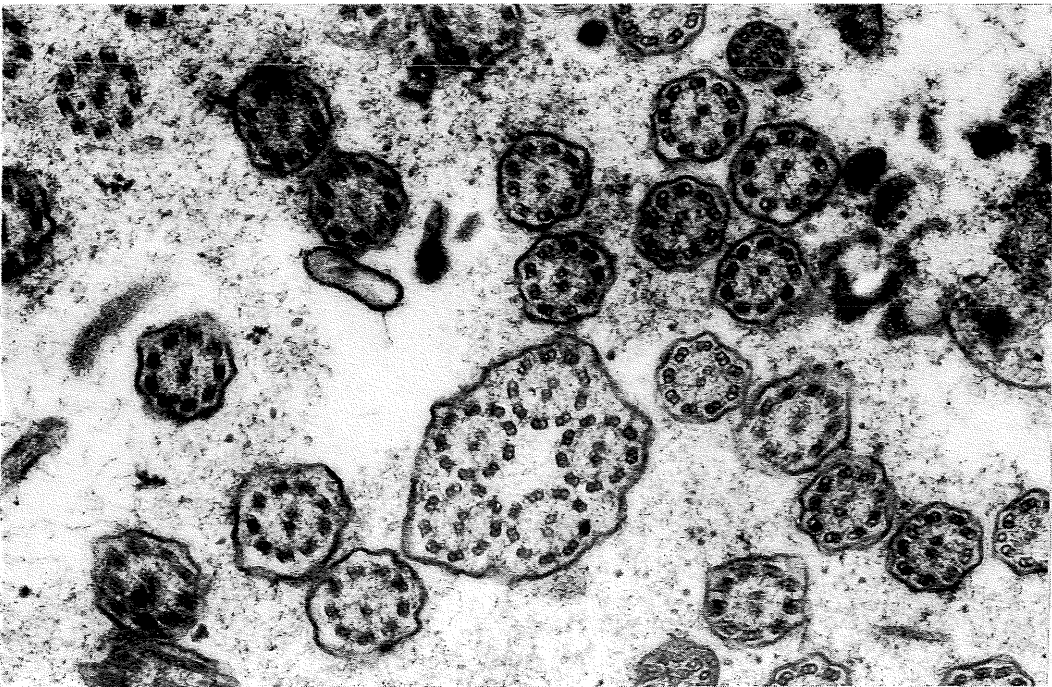


Fig. 5. Five 9+2 axonemes in a cilium

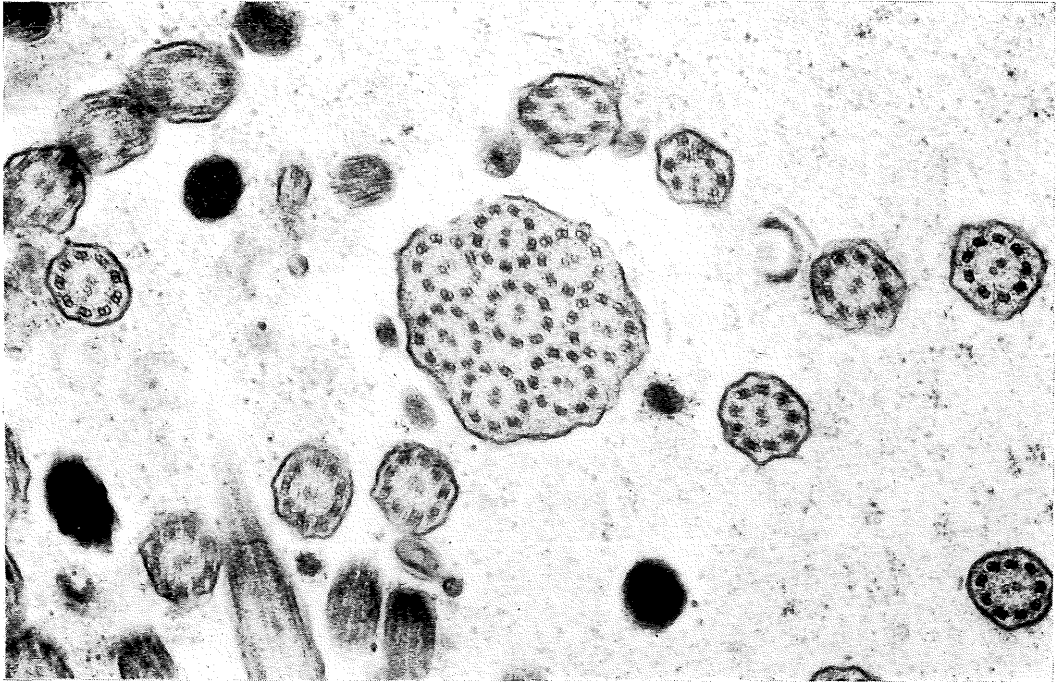


Fig. 6. Eight 9+2 axonemes in a cilium

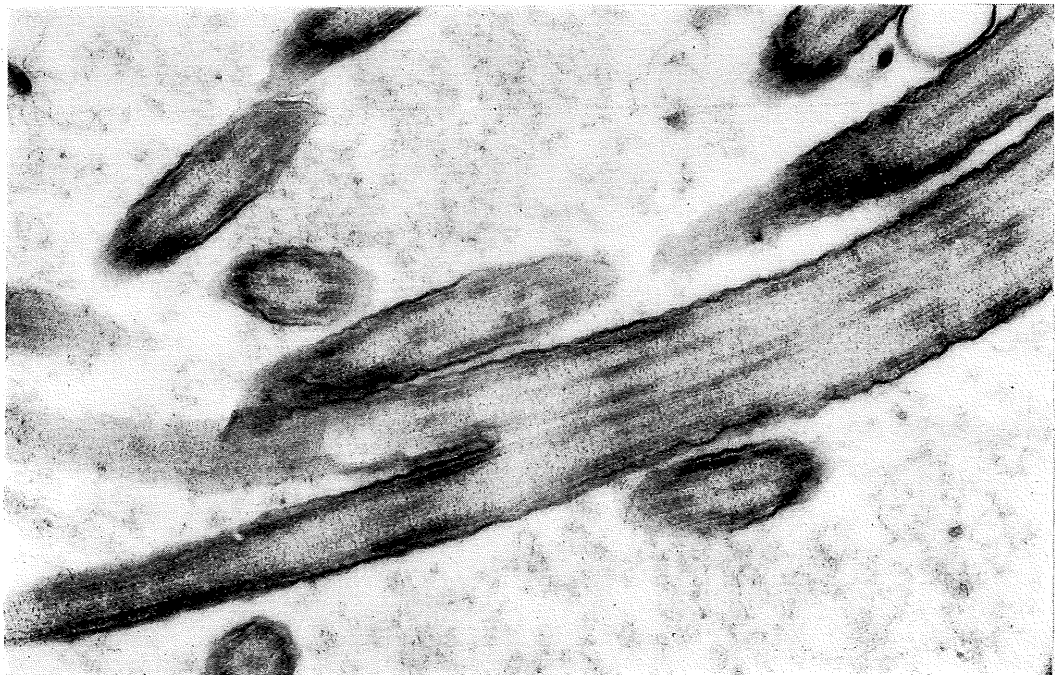


Fig. 7. Longitudinal section

Fig. 4 to 7. Cross sections of cilia showed many kinds of compound cilia