

## Clinical Features of *Mycoplasma pneumoniae* Pneumonia

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Clinical features in ninety-two cases of mycoplasmal pneumonia during the past seven years, which are forty-one percent of 226 primary atypical pneumonia cases in this study, are reported. Occurrence of the illness was closely related to age of the patients; it was generally higher in patients under thirty years of age at all seasons. The main clinical symptoms were cough, fever, rales, sputum, headache and sore throat. However, these common symptoms recognized in a variety of respiratory diseases were not particular to the diagnosis of mycoplasmal pneumonia, and it was often difficult to differentiate from pulmonary tuberculosis, chronic pneumonitis or bronchiectasis. Although a roentgenographic pattern characteristic of mycoplasmal pneumonia could not be recognized, the majority showed a "homogenous" or "flocculent" appearance. Therefore, the appropriate laboratory studies for isolation of the agents and/or the related serological tests have much importance to the diagnosis of this disease. The treatment with erythromycin seemed to be more effective than other antibiotics when using chest roentgenographic resolution, as the parameter of response.

### INTRODUCTION

Many studies in the clinical response of mycoplasmal pneumonia have been reported. Most of the reports have been studied with respect to diagnosis, ie. isolation, serological test, symptoms, physical findings, chest X-ray pattern. As the result of these, it has been

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suspected that pneumonia caused by *Mycoplasma pneumoniae* (*M. pneumoniae*) cannot be differentiated clinically from other causes of pneumonia (1, 2).

In this paper, ninety-two cases with *M. pneumoniae* pneumonia diagnosed and treated in our clinic for the past seven years were reported compared to clinical primary atypical pneumonia (PAP) of unknown etiology.

## MATERIALS AND METHODS

When the patients were suspected of having primary atypical pneumonia they were investigated for the following studies according to the orders in our pneumonia card after hospitalization.

**Bacteriologic studies:** For 3 days after the first medical examination, specimens of sputum were cultured in all patients. If the patients were treated with some antibiotic before starting the trials, culture was performed twenty-four hours after the antibiotic therapy was discontinued. If patients found it difficult to give proper specimens for the bacteriologic investigation, it was collected by aspiration through the vinyl tube in Metra's tube from the focal region. This was done even if the patient had slight fever.

Usually BTB, chocolate and blood agar plates were used for common bacteriologic studies, but, if mycosis of the lung was suspected, SABOURAUD'S solid medium was also used. Each patient's sputum was also tested using ZEEHL-NEELSEN'S staining and cultivated in OGAWA'S medium for 3 consecutive days to confirm the presence of tubercle bacilli.

**Mycoplasma studies:** Throat swabs from the patients were inoculated on each of two PPLO agar plates and broths. The growth of mycoplasma was observed at intervals during 14 days for the development of microscopic colonies on the agar plates and for colour change from red to yellow which showed the alteration of PH in the broth medium. When mycoplasma colonies were grown, it was identified to be *M. pneumoniae* by CLYDE'S paper disc diffusion method (3). The blood specimens were obtained at the first visit or admission of all patients, although it was not always suitable in the acute phase. Subsequently convalescent sera were collected on one or more occasions about 14 or 21 days later. Sera were tested for complement fixing antibody. The definite evidence of recent infection was established by our criteria in a preceding paper (4), if briefly stated; (a) An eight-fold or more rise between acute and convalescent sera, or (b) A four-fold rise, and reacted in a dilution of 1:64 or greater in the convalescent complement fixing antibody titer.

**Virologic studies:** As the evidence of recent infection of a virus only, serological tests against influenza virus A<sub>2</sub> and B (CF and HI), parainfluenza virus type 1 (CF), adenovirus type 3 and 21 (CF), echo virus type 2 and 9 (CF), coxsackie virus A type 9 and B type 3 (CF) were determined in all patients; these viruses were considered to be the etiological agents of viral pneumonia.

**Clinical studies:** The patient was asked about clinical symptoms, such as cough,

sputum, sore throat, nasal symptom, chest pain, fever, headache, chill, arthralgia, otalgia, and also examined in respect to swelling of throat and rales in chest at least once daily by a member of the mycoplasma group who kept records on our pneumonia card.

Routine laboratory studies: Erythrocyte sedimentation rates, total and differential leukocyte counts and cold haemagglutination tests were performed regularly once a week, chest roentgenograms twice a week. If it was required, c-reactive protein, mucopolysaccharide, lactic dehydrogenase, urinalysis, liver function tests were also determined. Anyone who was suspected bronchiectasis was immediately examined by bronchography or, if necessary, by bronchofiberscope.

In order to avoid a subjective view of only one doctor, roentgenographic films of the chest, particularly as to the point of position and pattern of the shadow, was classified by discussion by all members of mycoplasma study group.

## RESULTS

General description of the subjects: Three hundred fifty-eight of the 21,013 patients who attended the clinic of the second department in Nagasaki University School of Medicine during the period March 1965 to July 1972 were suspected initially of having clinical primary atypical pneumonia. Of these patients, 92 had mycoplasmal pneumonia, 134 had viral pneumonia or unknown etiologic PAP, and the remaining 132 patients, were diagnosed as having diseases due to other causes; particularly pulmonary tuberculosis, chronic pneumonitis, mycotic pneumonia, infiltrative type of pulmonary cancer. It was felt that pulmonary tuberculosis was most important disease to differentiate from primary atypical pneumonia in Japan.

Age and Sex: The distribution of patients as to age is shown in Table 1. Ninety-two of 226 patients who were diagnosed as having PAP were pneumonia caused by *M. pneumoniae*. That is 41% of the patients. The incidence of *M. pneumoniae* pneumonia was related more to the age group under thirty years. Fifty were males and forty-two were females.

Table 1 Age of patients with clinical primary atypical pneumonia (PAP)

Age	Total number of PAP	Cases with CF antibody rise against <i>M. pneumoniae</i> with or without isolation	Percentage for total PAP
0 - 5	27	12	44
6 - 10	40	25	63
11 - 20	38	21	55
21 - 30	35	17	49
31 - 40	24	8	33
41 - 50	29	4	14
51 -	33	5	15
Total	226	92	40.7

Occurrence of the illness: The month of admission of patients with mycoplasmal pneumonia and the patients who had contacted influenza virus as the primary etiologic agent of pneumonia without secondary complication is plotted on Figure 1. The outbreak of primary influenza pneumonia was observed between December and March corresponding to the epidemic periods of flu in Japan, but mycoplasmal pneumonia was observed almost equally throughout the year.

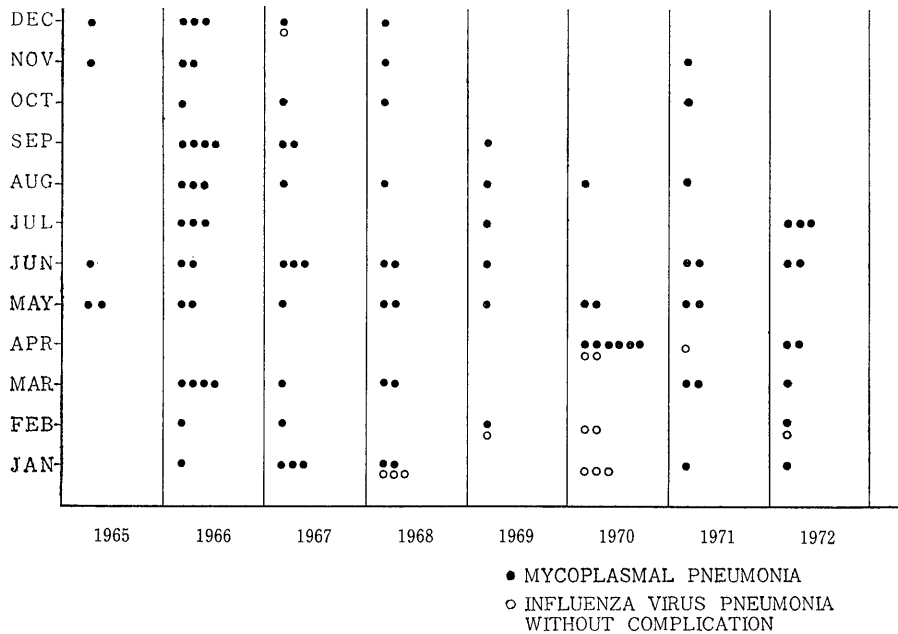


Fig. 1. Occurrence of *M. pneumoniae pneumonia*

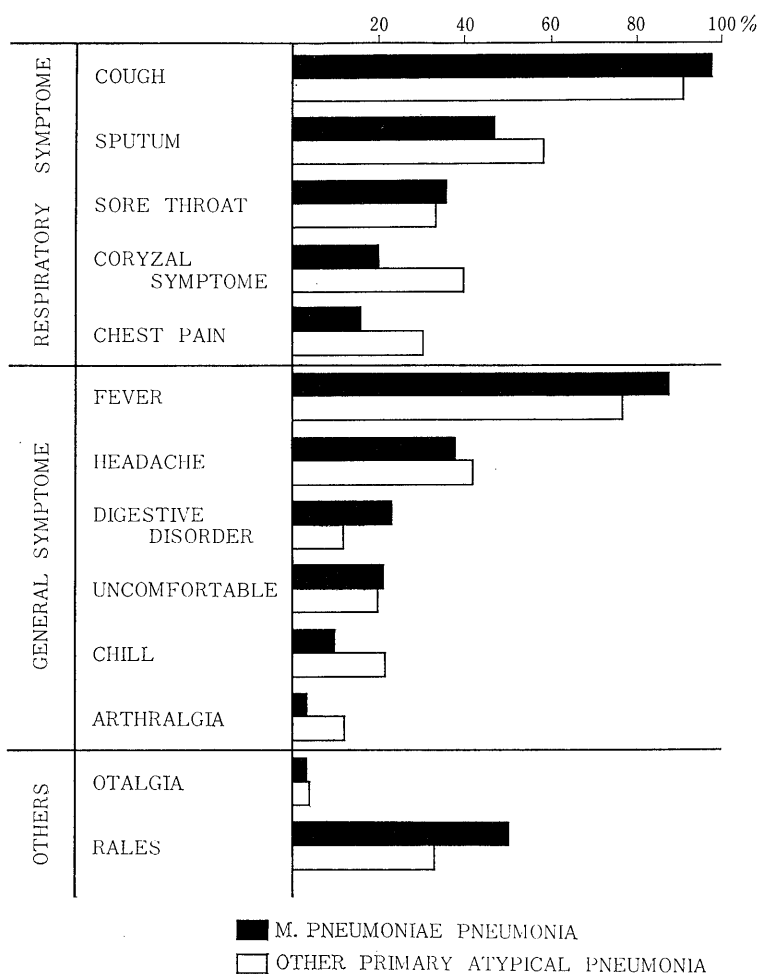
Serologic studies: The summary of serologic data is shown in Table 2. Twenty three of 134 mycoplasma-negative PAP demonstrated a four-fold or greater increase in antibody against one of viruses measured. In thirteen of these patients, it was assumed that these viruses played the etiologic role of pneumonia under clinical and epidemiological consideration. Nine of 92 patients with mycoplasmal pneumonia were noted to have four-fold or greater rise in virus antibody. Two patients had a dual infection clinically.

Bacteriologic studies: In the ninety-two mycoplasmal pneumonia patients 42.4 per cent (23 males and 16 females) yielded *M. pneumoniae*.

A heavy growth of microorganisms was obtained in the sputum or aspirated specimen cultures from thirteen patients as a whole. Of eleven organisms which were isolated from the patients with mycoplasma-negative PAP, 5 were *Diplococcus pneumoniae*, 4 were coagulase positive *Staphylococcus*, one was *Haemophilus influenzae* and one was *Streptococcus haemolyticus*. The organisms which were isolated from two patients with mycoplasmal pneumonia were *Klebsiella aerogenes*. One of these patients had been reported in detail as a case with suspected superinfection with *M. pneumoniae* and *Kl. aerogenes* (5). The

**Table 2** Serological response of patients with clinical primary atypical pneumonia (Total number 226)

Antigen	M. pneumoniae positive (92)	negative (134)	Total positive number	Percentage for total patients
Mycoplasma pneumoniae	92		92	40.7
Influenza virus { A	4	12	19	8.4
B	1	2		
Adenovirus	2	5	7	3.1
Echovirus { 2	0	0	3	1.3
9	1	2		
Coxsackie virus { A	1	0	2	0.9
B	0	1		
Parainfluenza virus	0	1	1	0.4



**Fig. 2.** Sign and symptoms of patients with clinical primary atypical pneumonia

remaining twelve patients did not have the definite clinical evidence of bacterial pneumonia in spite of a predominant growth of the microorganism in culture.

Clinical findings: In the description of clinical symptoms, mycoplasma positive cases were compared with mycoplasma negative PAP (Figure 2).

The majority of the patients with mycoplasmal pneumonia (97.8%) had experienced an attack of characteristic coughing towards morning, this persisted each morning until terminal stage of the illness. In 88.0 percent of these patients fever above 38°C was experienced during the maximal stage. Otalgia was observed in only four patients and redness of tympanic membrane by otologic examination was confirmed in three of these four. In addition, physical findings of the lung included dry rales, moist rales or both was detected in approximately 50 percent of these patients. Thirty-eight patients developed the illness after a few-days course of common cold symptoms including rhinorrhoea and sore throat. Fifty-two patients, however, suddenly started with the onset of two or more symptoms of cough, fever, chill and loss of appetite. Fortunately two patients were found to have shadows on the chest X-ray film in mass examination without any respiratory symptoms and it was confirmed after admission that these shadows were produced by *M. pneumoniae* infection.

Symptoms in patients with mycoplasma negative PAP were fairly similar to that of mycoplasmal pneumonia, although coryzal symptoms, chest pain, chills and joint pain presented in high incidence in negative PAP patients.

Laboratory studies: In one-third of the patients total leukocyte counts on admission were above 20,000, and this leukocytosis was maintained during the acute stage; usually 4 to 7 days. The majority of the remaining ranged from 4,000 to 10,000 per cu. mm. About one quarter of all the patients showed a neutrophilia and an increase in immature band forms. Erythrocyte sedimentation rates obtained on admission ranged from 8 to 128 mm per hour, and were significantly elevated in the majority of the patients. The shifting of the erythrocyte sedimentation rates and c-reactive protein were relatively reflected in the course of the illness. Serum cold haemagglutinin presented in 70.7 percent of the 92 mycoplasma positive PAP and in 28.4 percent of 134 mycoplasma negative PAP. It seemed clinically advisable that serum cold haemagglutination tests should be performed to confirm the diagnosis of mycoplasmal pneumonia.

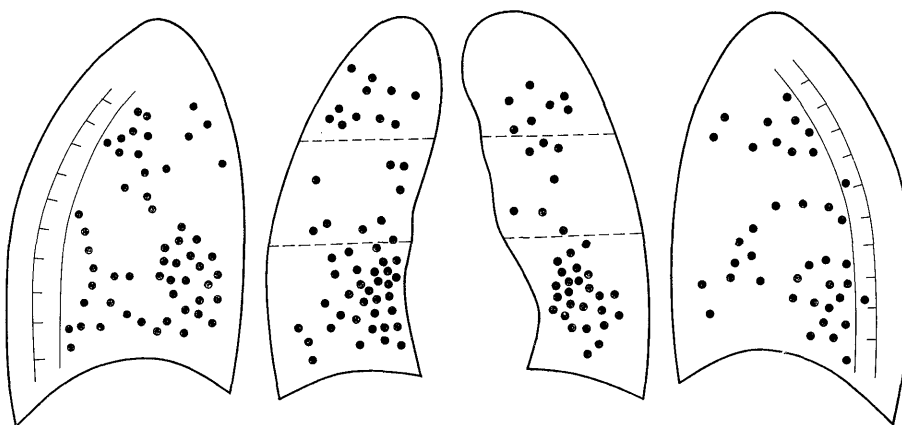
Chest roentgenogram: The central area of chest roentgenographic involvement in the patients with mycoplasmal pneumonia is marked with a black dot in Figure 3. The number of dots is seen most in the right lower lung field, followed by the left lower and the right upper. Further, in about 90 percent of the patients the shadow on the films made in the antero-posterior position was confined to one lung field, but the remainder extended to two or more lung fields; mostly unilateral middle and lower fields or bilateral hilus. In the lateral view, the most frequent shadow was located along the bronchus from hilus. It was also frequently located at S<sub>4</sub>, S<sub>5</sub>, and S<sub>8</sub>, S<sub>10</sub> in right side and S<sub>10</sub> in left side in the pulmonary segment.

When shadows were assorted by CRYSLER'S classification (7) based on the roent-

genographic characteristics of the patients with primary atypical pneumonia, 43.4 percent of all patients occupied a "homogenous" pattern, 40.8 percent a "flocculent or dense structural" and 15.8 percent a "homogeneous flocculent" (Table 3.). This percentage was just similar to CRYSLER'S results. Of all patients, atelectasis occurred in 7 patients and pleural effusion in 2 patients.

Effects of antibiotics: It is well known that *M. pneumoniae* is sensitive to erythromycine, tetracyclines and chloramphenicol but resistant to cephalosporin C derivate or penicillin. If the patient was suspected to have clinical PAP, one or more of the following antibiotics were chosen by the physician in charge.

- a) a macrolide derivate, mostly erythromycine 1.2 g daily, three times, orally.
- b) tetracycline 1.2 g daily, three times, orally.
- c) chloramphenicol 1.5 g daily, three times, orally.
- d) tetracycline 1.2 g + erythromycine 1.2 g daily, three times, orally.
- e) aminobenzyl-penicillin 1.5 g or cephalixin 2.0 g daily, twice, orally.
- f) conservative therapy without antibiotics.



only main shadow was marked in the case  
of both involved

Fig. 3. Position of chest roentgenographic Shadow in  
the patients with mycoplasmal pneumonia

Table 3 Chest roentgenographic pattern by Crysler's classification

Homogeneous	Homogeneous with structural accentuation	Cotton wool	Flocculent	Flocculent with structural accentuation	Dense structural accentuation	Homogeneous flocculent
22.4%	9.2%	11.8%	10.5%	10.5%	19.7%	15.8%
43.4%			40.8%			15.8%
*(46.4%)			(39.7%)			(13.9%)

\* indicated the result by Crysler

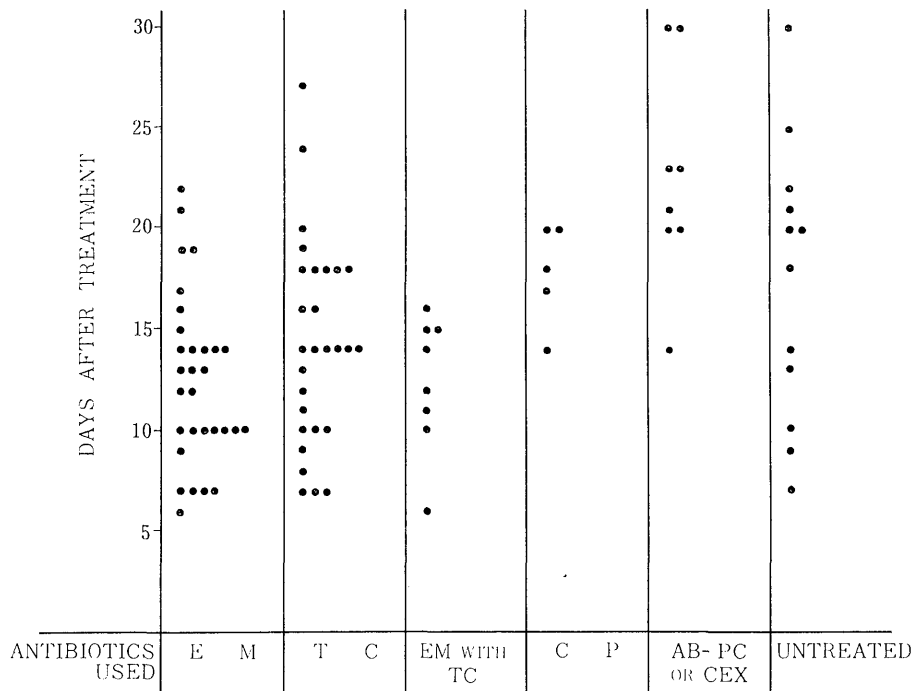


Fig. 4. Persistence of the shadow after treatment start

Table 4 Frequency of mycoplasmal pneumonia in primary atypical pneumonia (by Kitamoto, 1970)

patient's age	number of Patients with PAP	percentage against PAP	period tested	method	country	reporter
university students	119*	22	1953-60	FA	U.S.A.	Evans
adults	429*	3	1962-63	CF	U.S.A.	Mufson
all ages	320*	33	1961-66	FA	Holland	Hers
"	112*	10	1962	CF	England	Goodburn
"	246*	16	1962-63	CF	Finland	Jansen
"	107*	33	1962-63	CF	Sweden	Biberfeld
"	63*	38	1962-64	CF	England	Andrews
"	360*	12	1963-64	CF	U.S.A.	Alexander
"	164*	11	1964-65	-	Germany	Witzleb
mainly children	1445	1.8-28.1	1967-68	CF	Japan	Niitsu
adults	97	37	1947-59	FA	U.S.A.	Cook
all ages	-	30-60	1957-61	-	U.S.A.	Parrot
"	215	20	1962-63	FA	U.S.A.	Grayston
"	639	37	1963-68	CF	Japan	Kitamoto
"	84	27	1964-66	CF	Japan	Masuda
"	226	41	1965-72	CF	Japan	Hara

\*These subjects included the patients with purulent pneumonia



The doses mentioned above correspond to the adult, it is varied with or by individual patient response. As a rule, these antibiotics were administered under strict attention up to 1 week after the clearing of the shadow on X ray film.

One patient suspected of having an infection with *M. pneumoniae* and *Kl. aerogenes* was excluded from this study because of the use of some other antibiotics. Of the ninety-one patients, as noted in Figure 4, 30 were treated with a macrolide derivate, 28 with tetracycline, 5 with chloramphenicol, 8 with a macrolide derivate plus tetracycline and 8 with aminobenzyl-penicillin or cephalixin. Twelve patients were treated with only some sedative but not with antibiotics.

In order to compare the effect of each antibiotic for mycoplasmal pneumonia the shadow presented in the beginning of the treatment was observed according to the method described by RASCH et al (8). The persistence of the shadow even after treatment was prolonged from the shortest treatment group with macrolide derivate as well as with macrolide plus tetracyclin to the longest treatment groups with aminobenzyl-penicillin or cephalixin. The antibiotic-free group was situated between these two. A majority of patients treated with aminobenzyl-penicillin or cephalixin were initially considered to have bacterial pneumonia and were referred to our clinic in the final stage of the illness.

## DISCUSSION

It has been nearly a decade, since the name *Mycoplasma pneumoniae* was given to an organism thought to be the etiologic agent of primary atypical pneumonia (9). The research of clinical and epidemiological nature of this mycoplasmal infection, of course, has been supported by the experimental observation of volunteers made by CHANOCK (10) and RIFKIND (6).

It is well known that the pattern of *M. pneumoniae* infection is endemic(11,12,13), not pandemic, and therefore intimate and prolonged contact is required (1, 14). This was recognized to be the infection among small groups of people such as families(15-22), military recruits (23) or submarine crews (24). Such epidemiological problems including occurrence of the endemic, reinfection and carrier state of the mycoplasmosis has been discussed too, by us, previously (4). At this time, the clinical features of ninety-two cases suffering from *M. pneumoniae* pneumonia were described.

The patient with mycoplasmal pneumonia occupied between 1.8% and 60% of patients with primary atypical pneumonia as shown Table 4, which was summarized by KITAMOTO (25). Although our results were situated in a high position, it was considered that this frequency would be changeable depending upon the method of the investigation or the existence of the prevalence, and so forth.

The clinical illness caused by this organism is usually called primary atypical pneumonia. However, CHANOCK *et al* has stated some characteristics of mycoplasmal pneumonia (26): it generally has (a) a longer incubation interval (2-3 weeks), (b) longer duration if untreated, (c) more headache and earache, (d) less coryza, (e) rales in approxi-

mately 50 to 80 percent of patients. In our data, the incubation period could not exactly be proved, because the patients were attending an out-patients clinic. Surely the coryzal symptom was less in the mycoplasmal patients than the mycoplasma negative patients and moist rales in more than half cases was observed in 51 percent of the patients. Conversely, headache and earache showed a same percentage in mycoplasma positive and negative PAP. Cough occurred in about 98 percent of patients persisted until terminal stage of the illness as described by KINGSTON (27).

The roentgenographic findings in the patients diagnosed as mycoplasmal pneumonia have been reported (29–33). However, when the abnormal pulmonary X-ray findings seen in the patient with mycoplasmal pneumonia were compared with those observed in mycoplasma negative pneumonia (28) and with those observed in usually called primary atypical pneumonia reported by CRYSLER, they had almost similar incidence. Therefore, it could be stated that pulmonary roentgenographic pattern in the patients caused by the organism cannot be differentiated from that of patients by other etiologic agents as noted by GEORGE, HEBERT and ZWAD (29, 30, 32). Although small number of the patients had evidence of roentgenographic findings of atelectasis or pleural effusion it was reported that these were not peculiar findings to mycoplasmal pneumonia (29, 30, 31).

As the patients suffering from the pneumonia caused by *M. pneumoniae* were not treated by double blind method, the effect of antibiotics for this disease may not always reflect true evaluation. Yet, macrolide derivatives mainly erythromycin, alone or combined with tetracycline resolved the abnormal shadow in the shortest stage averaging about 12.5 days. Contrarily, the average time required for roentgenographic clearing was 17.4 days in untreated group and 22.6 days in the treated group with aminobenzyl-penicillin or cephalixin although this group included many severe cases. It was observed by SMITH *et al* that the organism was not eradicated by therapeutic doses of erythromycin or tetracycline (34). Experimental studies by us in the hamster showed that the organism remained in the lungs for as long as 16 days in spite of treatment with erythromycin or tetracycline (35). Similar results were reported by SLOTKIN (36) in a study for prophylactic approach *in vivo* and *in vitro*. Our results in clinical treatment corresponded to the results *in vitro* as did the report by RASCH *et al* (8) and KINGSTON *et al* (27), but the determination of effect in the treatment with antibiotics for mycoplasmal pneumonia due to the roentgenographic resolution could not be correlated to that due to the eradication of the organism.

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