STUDIES ON PRIMARY ATYPICAL PNEUMONIA.

I. CLINICAL FEATURES AND RESULTS OF LABORATORY INVESTIGATIONS[1, 2]

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"Primary atypical pneumonia, etiology unknown" (1) is one of many terms used to designate an acute respiratory infection which has been widely prevalent in recent years. The illness is characteristically gradual in onset, with constitutional as well as respiratory symptoms, and pulmonary changes more manifest in roentgenograms than by physical examination. The course of illness varies considerably in duration and severity. Complications are uncommon and although convalescence is frequently protracted the illness almost invariably terminates with complete recovery. Therapy with sulfonamide drugs is not effective.

Contemporary interest in this form of pneumonia was aroused by several fairly recent reports (2 to 4), although one author (5) had observed patients with a similar illness several years earlier. Numerous other descriptions and investigations of primary atypical pneumonia have since been published, and have been reviewed recently (6 to 9). In some of these reports, unusual outbreaks of acute respiratory illnesses described during the past century were cited to show that primary atypical pneumonia is probably not a new disease. Nevertheless, it is apparent from these reports that, in recent years, the incidence of the disease has actually increased. The rate of its occurrence in the civilian population is not known. In the armed forces, however, it has appeared to be more prevalent than the pneumococcal pneumonias and the total number of man days lost as a result has been considerable.

The term "primary atypical pneumonia" has been useful in distinguishing the syndrome under discussion from clinically similar illnesses due to known infectious agents (10) such as *Rickettsia diaporica* (11) and members of the psittacosis group of viruses (12, 13).

Although primary atypical pneumonia has been frequently referred to as "virus pneumonia" and most investigators have considered it to be of non-bacterial origin, the causative agent, or agents, in the majority of cases has remained obscure. The recovery of a number of different viruses (14 to 18) from certain patients with primary atypical pneumonia has been reported but the importance of any of these agents in the pathogenesis of the disease has not been established.

An investigation of primary atypical pneumonia has been carried out continuously at the Hospital of The Rockefeller Institute since February, 1942. Because of circumstances which afforded extensive clinical as well as laboratory facilities, it was possible while investigating the pathogenesis of primary atypical pneumonia to conduct also an appraisal of its clinical aspects. An effort was made to correlate these two lines of investigation and to study each patient in as comprehensive a manner as possible

Recently, a non-hemolytic streptococcus, isolated from the lungs of 2 patients who died of primary atypical pneumonia, was found to react with sera obtained, during convalescence, from other patients with this illness but did not react with sera obtained during the acute stage of the disease (19). For convenience in reference, this

[1] The Bureau of Medicine and Surgery does not necessarily undertake to endorse the views or opinions which are expressed in this paper.

[2] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The Rockefeller Institute for Medical Research.

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microorganism has been designated streptococcus MG. Because of the possibility that streptococcus MG might have more than an incidental association with primary atypical pneumonia, the properties of this microorganism and its relation to the disease were investigated. The bacteriological and serological characteristics of streptococcus MG are described in separate communications (20, 21). The special techniques for isolating streptococcus MG from the respiratory tract of human beings and an extension of the original observations concerning the relation of this microorganism to primary atypical pneumonia are described in the accompanying paper (22).

It is the purpose of the present paper to describe the clinical features of primary atypical pneumonia as observed in patients studied in the Hospital of The Rockefeller Institute, to present the results of various investigations pertaining to the disease, and to correlate some of these findings with the studies concerning streptococcus MG which have been referred to above (20 to 22).

From August 1, 1942, to March 2, 1944, 180 patients were admitted to this hospital with acute respiratory infections suspected to be primary atypical pneumonia. In each case, a careful and detailed record was made of the clinical features. Roentgenograms of the chest were made at frequent intervals and numerous clinical laboratory studies were carried out. In addition, samples of serum were obtained repeatedly throughout the illness and were stored at 4° C. for use in serological tests. Specimens of plasma, sputum, and nasopharyngeal washings, as well as specimens of pleural or cerebrospinal fluid, were examined immediately after they were obtained and portions of each specimen were preserved at −70° C. for use in subsequent investigations.

From the completed records of these 180 patients, 106 were selected on the basis of clinical and laboratory criteria as representative examples of primary atypical pneumonia. The criteria used for selection permitted the inclusion of only those patients who showed each of the following findings: (*1*) acute febrile respiratory disease; (*2*) pulmonary consolidation demonstrable by x-ray; and (*3*) adequate clinical and laboratory evidence that the pneumonia was not due to pneumococcus or other microorganisms of recognized pathogenicity.

Ninety-five of the patients were male and 11 were female. All patients were young adults. These patients came from widely separated areas and had been exposed to multiple and diverse sources of infection. Nevertheless, as a group, they exhibited a remarkable degree of clinical homogeneity.

CLINICAL FEATURES

The clinical features of primary atypical pneumonia, as observed in these 106 patients, were on the whole similar to those which have been described in other reports. The onset of illness was gradual in 73 per cent of the patients and, in contrast to lobar pneumonia, was usually ill-defined. Constitutional symptoms generally preceded those referable to the respiratory tract. In many instances, the initial complaint, variously described by the patient, suggested a combination of lassitude, weakness, and fatigue.

TABLE I

Symptoms in 106 patients with primary atypical pneumonia

	Symptoms	Patients	
		Number	Per cent
General	Headache	69	65
	Malaise	65	61
	Chills or chilliness	63	59
	Generalized aches	30	28
	Anorexia	37	35
	Nausea	30	28
	Vomiting	25	24
Respiratory	Cough	104	98
	Sputum	87	82
	Bloody sputum	27	25
	Sore throat	32	30
	Chest pain		
	Substernal	25	24
	Lateral	16	15
	Epistaxis	16	15
	Dyspnoea	5	5

In Table I, the commoner symptoms have been listed, together with the frequency of their occurrence. Chills, fever, headache, and cough developed early and occurred frequently. Shaking chills were rare but sensations of chilliness, sometimes recurring, were experienced by 59 per cent of the patients. Headache, usually generalized but sometimes predominantly frontal, occasionally associated with photophobia, and ranging from mild to extremely severe, oc-

curred in 65 per cent of the patients. Aching of the trunk and extremities was present in only one-fourth of the patients and as a rule was mild. About a third of the patients exhibited an appreciable degree of anorexia and nausea. Vomiting occurred at some stage of illness in one-fourth of the patients but this symptom was never a conspicuous or severe manifestation of the disease.

Cough, one of the most constant and characteristic features of primary atypical pneumonia, was present in all but 2 of the 106 patients. In some instances, this was the first symptom to appear; in others, it developed gradually after a lapse of several days. Frequently, it became paroxysmal and exhausting. Coughing, although dry at first, was ultimately productive of sputum in 82 per cent of the patients. The sputum of one-fourth of the patients contained blood, usually, however, only as streaks or traces. Grossly bloody or "rusty" sputum was uncommon. Sore throat when present was rarely severe, and, in many instances, appeared to result from the irritation of coughing.

In association with the cough, about one-fourth of the patients experienced dull, burning, or oppressive substernal discomfort. Less frequently, sharper pains developed which were referred to the thorax laterally.

Epistaxis occurred in 16 patients and syncope in 3. Several patients complained of transient numbness and tingling of the extremities. Abdominal pain was only an occasional and then unimpressive complaint.

The results of physical examinations of these patients are summarized in Table II. On admission, most of the patients did not appear to be very ill. An elevation of temperature was noted during hospitalization in all but 5 instances. Cyanosis was rarely present, and herpetic lesions were observed in only 3 instances. Respirations were usually normal in rate and seldom labored. Tachypnea was seen in only 14 of the more severely ill patients. Relative bradycardia, however, observed in over two-thirds of the patients, was a frequent finding during the early febrile phase of illness, and a feature of considerable diagnostic assistance in distinguishing clinically between this syndrome and pneumococcal pneumonia. Significant tachycardia was infrequent and, when present, usually developed during convalescence.

TABLE II

Abnormal physical signs in 106 patients with primary atypical pneumonia

Physical signs	Patients	
	Number	Per cent
Fever	101	95
Nasal congestion	60	57
Pharyngitis	73	69
Cervical adenopathy	25	24
Pulmonary signs	104	99
Dulness	57	54
Altered breath sounds	74	70
Râles	99	93
Friction rub	7	7
Fluid	1	1
Bradycardia	72	68
Tachycardia	8	8
Tachypnoea	14	13
Cyanosis	12	11
Signs referable to the central nervous system	6	6
Palpable spleen	1	1

Nasal congestion and mild pharyngitis were noted respectively in 57 and 69 per cent of the patients. Cervical lymph nodes were enlarged in one-fourth of the patients, but usually were not prominent or tender.

Physical signs of pulmonary disease, although much less definite than in lobar pneumonia, were nevertheless detected at some stage of illness in all but 2 of the 106 patients. Dulness to percussion, usually of slight degree, was noted over the affected area in more than half of the patients. Alterations in the breath sounds, usually harshness or diminished transmission, occurred in 70 per cent of the patients. On the other hand, breath sounds of tubular quality and pectoriloquy were rarely heard. Râles, usually fine and subcrepitant during the early stages of illness, later coarse and more moist, were detected in 93 per cent of the patients. Often râles could be heard only after coughing or at the end of deep inspiration. A pleural friction rub was heard in 7 instances and, in 1 patient, signs of pleural effusion were detected. A few patients with severe headache had slight stiffness of the neck. One patient briefly lost the power of ocular accommodation. The spleen was palpable in only 1 instance. Abdominal distension, so common in lobar pneumonia, was conspicuously absent. No other relevant abnormalities were noted on physical examination.

The clinical course of illness in the present

group of patients was extremely variable. All recovered, but it was not possible to predict accurately either the duration or the severity of illness in any given case. In the total group of patients, elevations of temperature to 100° F. or more were present for an average of 10.1 days, ranging in individual patients from 0 to 41 days. Physical signs of pneumonia were present for an average of 12.8 days, but also ranged from 0 to 41 days. The maximum recorded temperature averaged 103.5° F. with a range of 99 to 106° F. The charted temperature curves of individual patients also showed great variation. The commonest type of curve was moderately remittent, and rarely was either high persistent fever or markedly intermittent fever seen. Defervescence was usually by lysis over a period of more than one day. Hospitalization was required for an average of 33 days with a range of 10 to 73 days.

Complications were rare and usually not of great significance. Pleuritis occurred in 6 patients. In only 1, however, was the accumulation of fluid sufficient to warrant thoracentesis. In the others, the amount of fluid was evidently small and, in several, it was located principally in the interior fissures. Acute sinusitis developed in 8 patients and non-suppurative otitis media occurred twice. One patient had severe stomatitis and gingivitis. Another patient, during convalescence from primary atypical pneumonia, contracted lobar pneumonia due to pneumococcus Type XIV, evidently by contact, and in both infections, the left lower lobe was the site of consolidation.

Although no systematic investigation of the therapeutic value of sulfonamides in primary atypical pneumonia was carried out, 32 patients in this study received sulfathiazole or sulfadiazine during the course of illness. Of these, 16 received an adequate therapeutic trial over a period of 4 to 9 days, with total dosages of 21 to 50 grams. Ten patients showed no evidence of a therapeutic response. In 6 patients, the temperature returned to normal within 72 hours of the initiation of treatment, but in all 6, defervescence occurred between the sixth and tenth days of illness. Moreover, in 2 of these patients, the fall in temperature occurred within 24 hours, before an adequate dose had been given and before a response could reasonably be expected. These findings are in agreement with previous observations that sulfonamides do not obviously benefit patients with this disease.

X-RAY FINDINGS

X-ray films of the lungs, taken at frequent intervals throughout the course of illness, showed evidence of more extensive pulmonary lesions than the findings on physical examination would have led one to expect. Data concerning the site, extent, and duration of pulmonary consolidation as determined by multiple serial roentgenograms on each patient are presented in Table III. In this study, the word "consolidation" has been used in a broad sense to designate findings thought to represent pneumonic involvement of the lung parenchyma. In referring to x-ray films of the lung, this term is used irrespective of the extent or density of the pneumonic shadow.

TABLE III

Distribution, extent, and duration of pulmonary consolidation as determined by serial x-ray films in 106 patients with primary atypical pneumonia

	Patients	
	Number	Per cent
Lobe involved		
Left lower	66 (18)*	62.2 (16.9)
Left upper	19 (2)	17.9 (1.9)
Right lower	64 (20)	60.3 (18.9)
Right middle	22 (3)	20.7 (2.8)
Right upper	25 (7)	23.5 (6.6)
Number of lobes involved		
1	50	47.1
2	38	35.8
3	8	7.5
4	4	3.8
5	6	5.7
Duration of consolidation		
1 week	9	8.4
2 weeks	51	48.1
3 weeks	25	23.4
4 weeks	11	10.3
5 weeks	8	7.5
6 weeks	2	1.9
7 weeks	0	

* Numbers in parentheses indicate patients in whom the designated lobe was the only site of pulmonary consolidation.

As shown in Table III, the site of pulmonary consolidation was most frequently in the lower lobes and the incidence of involvement was almost identical on the 2 sides. Consolidation was present in the left and right lower lobes in 62.2 and 60.3 per cent of patients, respectively. Each of these lobes was the only site of consolida-

tion, however, in 16.9 and 18.9 per cent of patients, respectively. Consolidation was present in the left and right upper lobes and the right middle lobe in 17.9, 23.5, and 20.7 per cent of patients, respectively. On the other hand, each of these lobes was the only site of consolidation in 1.9, 6.6, and 2.8 per cent of patients, respectively.

Pulmonary consolidation as observed in roentgenograms was confined to a single lobe in 50 patients, located in one of the lower lobes in 38 patients, in one of the upper lobes in 9 patients, and in the middle lobe in 3 patients. Pulmonary consolidation occurred in more than one lobe in 56 patients. Two lobes were involved in 38 patients, 3 lobes in 8 patients, 4 lobes in 4 patients, and all 5 lobes in 6 patients. The average number of lobes involved for all patients was 1.85.

In some instances, multiple lobes were involved simultaneously, in others consolidation extended from one lobe to another or new shadows appeared in one or more lobes during the course of illness. Occasionally, fresh areas of consolidation appeared while other areas were undergoing resolution, and consolidation was observed to recur in the same site or to reappear in another area after the initial lesion had cleared. Thickening of the interlobar septa, occasional small collections of fluid in the interlobar fissures or in the costophrenic angles, and, in films of one patient, definite pleural effusion were also observed.

The individual pulmonary lesions as viewed in roentgenograms showed extraordinary variation in density as well as in distribution. Usually, an area of pneumonic consolidation was present in the initial film of the chest taken at the time of admission, even as early as the first or second day of illness. In a few patients, evidence of pneumonia was not present on admission but appeared subsequently. In some of these patients, consolidation first appeared as an isolated area well out in the lung parenchyma without obvious connection with the hilar shadow. In most instances, however, the initial consolidation made its appearance and was most dense at the hilum, spreading and becoming less dense toward the periphery of the lung. The borders of the consolidated areas were usually irregular, ill-defined, and not always confined by interlobar boundaries. Sometimes the shadow was present only as a diffuse haze; in other instances, it was quite dense. Only rarely, however, was the density or extent of consolidation in a given lobe comparable to that seen in lobar pneumonia. In other instances, consolidation was mottled and sometimes the appearance of small abscess cavities was suggested. Infiltrations radiating from the hilum and involvement of the upper lobe resembled tuberculosis even more frequently, and other lesions, especially in the lower lobes, simulated bronchiectasis. The relative rapidity with which the lesions cleared in primary atypical pneumonia assisted in excluding a diagnosis of chronic pulmonary disease. Other forms of pneumonia could not be distinguished from primary atypical pneumonia in a given case on the basis of roentgenograms alone.

Resolution of the consolidated areas was observed to occur in several ways. In most instances, clearing proceeded from the periphery of the lung toward the hilum but occasionally resolution progressed in the reverse direction. Clearing was also observed to occur by progressive reduction in the size of the affected area and by a diminution of density until no evidence of consolidation remained. In many instances, during the process of resolution, the affected area assumed a diffusely mottled appearance. Frequently, after all parenchymal involvement was thought to have disappeared, the bronchovascular markings remained prominent.

In this group of patients, the duration of consolidation in roentgenograms was arbitrarily calculated as the interval from the onset of illness to the last day on which evidence of parenchymal involvement was still visible. As recorded in Table III, pulmonary consolidation had disappeared by the end of the second week of illness in more than half the patients and by the end of the third week in 80 per cent of the total number. The average duration of consolidation as determined by serial roentgenograms was 14.2 days with a range of 3 to 41 days.

Although in the present study, roentgenological evidence of pulmonary consolidation was established as one of the essential criteria for a diagnosis of primary atypical pneumonia, it

should be emphasized that the x-ray shadows observed were not distinctive of this disease syndrome exclusively and a diagnosis of primary atypical pneumonia could not be made on the basis of roentgenological evidence except in conjunction with clinical and laboratory findings.

CLINICAL LABORATORY FINDINGS

The total leukocyte count on admission and at various intervals thereafter was usually normal or only slightly elevated. This was another helpful feature in distinguishing primary atypical pneumonia from pneumonia due to pneumococci or other bacterial agents in which leukocytosis characteristically occurs. Data concerning the total leukocyte counts in the present group of patients are summarized in Table IV.

The total leukocyte counts recorded upon the 106 patients with primary atypical pneumonia during each week of illness were grouped in 4 categories on the basis of their magnitude. These included total counts of less than 5000, those of 5000 to 10,000 considered to represent the normal range, those from 10,000 to 15,000, and those of more than 15,000.

It is apparent that throughout the course of illness as measured in weeks, considerably more than half the total leukocyte counts were within the normal range, and two-thirds or more of the counts were less than 10,000. Leukopenia was relatively infrequent and never extreme. The lowest recorded count of 3300 was observed in the second week of illness. Total leukocyte counts above normal were in most instances between 10,000 and 15,000. Counts of more than 15,000 occurred during the first 3 weeks of illness but were uncommon. The highest count noted was 25,800 and occurred in the second week of illness. Sudden and unexplained shifts in the total counts sometimes occurred. Usually, however, in individual patients, neither high nor low counts were sustained on repeated examinations. The differential leukocyte pattern as observed in these patients was within normal limits.

The erythrocyte sedimentation rate was almost always increased during the acute phase of illness, and the accelerated rate usually persisted for some weeks during convalescence. A 5.0 ml. specimen of blood was collected in a tube containing dried potassium and ammonium oxylate and, within an hour, was transferred to a calibrated 100 × 3 mm. tube for the test. Readings were made at the end of 1 hour without correction for hematocrit, inasmuch as significant anemia was rarely present. The maximum rate was less than 10 mm. per hour in 4 per cent of patients, 10 to 19 in 2 per cent, 20 to 29 in 13 per cent, 30 to 39 in 22 per cent, 40 to 49 in 49 per cent, 50 to 59 in 9 per cent, and more than 60 in 1 per cent. A sedimentation rate of more than 15 mm. in 1 hour persisted on the average for 28.5 days with a range of 9 to 73 days. In a few instances, the sedimentation rate remained or became normal while the patient was still acutely ill. This observation was amply confirmed but not satisfactorily explained.

The urine was usually normal. Slight or moderate albuminuria was noted during the acute phase of illness in 22 per cent of the pa-

TABLE IV

Total leukocyte counts in 106 patients with primary atypical pneumonia

Total leukocyte count	Percentage of leukocyte counts* per week of illness									
	Week of illness									
	1	2	3	4	5	6	7	8	9	10
<5,000	5.9	8.0	1.9	9.7	5.9	13.3				
5,000 to 10,000	66.7	57.3	66.0	74.2	88.2	80.0	77.0	50.0	100.0	100.0
10,000 to 15,000	26.2	29.3	22.6	16.1	5.9	6.7	23.0	50.0		
>15,000	1.2	5.3	9.4							
Number of patients	84	75	53	31	17	15	13	4	1	2

* Only one count per patient per week was included in this analysis.

tients. Examination of the urinary sediment revealed granular or hyaline casts and transient occult hematuria in 10 and 8 per cent of the patients, respectively. Three of the 9 patients with microscopic hematuria had previously received sulfonamide therapy.

Lumbar puncture was done only when severe headache and meningismus were present. Specimens of cerebrospinal fluid from 6 patients were examined. Two contained lymphocytes (less than 50 per c. mm.) and gave weakly positive tests for protein. The other 4 fluids were normal.

ELECTROCARDIOGRAMS

Serial electrocardiograms [5] were taken on 50 of the patients with primary atypical pneumonia, none of whom gave a history of previous cardiovascular disease. No significant deviations from normal were detected during any stage of the illness from the third through the thirtieth day after onset. Specifically, there was no increase in the P-R interval, no elevation or depression of the S-T segment, and no T-wave change.

BIOCHEMICAL STUDIES

Biochemical assays [6] were carried out upon specimens of blood and urine from a number of representative patients. It was found that the icteric indices, prothrombin, serum CO_2, serum chloride, and plasma protein levels were within normal limits. Plasma carotene and vitamin A levels were reduced but only to a degree commonly encountered in other acute infectious diseases. As previously reported (23), chloride balance studies indicated that there was no striking disturbance of chloride metabolism, and plasma α-amino acid levels were found to be within the normal range. These latter two findings serve additionally to distinguish this syndrome from pneumococcal pneumonia, in which chloride metabolism is usually disturbed and the plasma α-amino acid levels are significantly reduced (24).

[5] Lt. C. G. Neumann (MC), U.S.N.R., kindly analyzed the electrocardiograms.

[6] Lt. Cdr. K. Emerson, Jr. (MC), U.S.N.R., Dr. C. L. Hoagland, Lt. Cdr. R. A. Phillips (MC), U.S.N.R., and Lt. Cdr. R. E. Shank (MC), U.S.N.R., kindly performed these analyses.

BACTERIOLOGICAL FINDINGS

The bacteriological flora of the nasopharynx and sputum was studied in each patient and an effort was made to obtain both qualitative and quantitative data. A culture of the blood was obtained from every patient at the time of admission and at intervals thereafter when indicated.

The cultures of the nose and throat in these patients yielded a variety of microorganisms. In cultures from occasional patients, one or another bacterial species appeared to predominate; but in the group as a whole, the bacterial flora appeared to be quantitatively and qualitatively similar to that commonly found in the upper respiratory passages of normal persons. The sputum of these patients also contained a variety of microorganisms, but, by ordinary methods of culture, no one species was found to be conspicuously or consistently present in specimens from the total group.

When pneumococci, streptococci, or *H. influenzae* were isolated from any source, an attempt was made to obtain specific identification by serological methods. The results are summarized in Table V.

Pneumococci were isolated from 54 per cent of the patients but in only 7 per cent was it possible to identify the organisms in the sputum directly by the Neufeld quellung technique. In most instances, pneumococci were isolated and identified following the inoculation of sputum into mice. Twenty-six different types of pneumococci were obtained from 57 of the 106 patients. It is noteworthy that pneumococci of types I and II, those most commonly associated with lobar pneumonia, were not found in any of the patients in this group. The distribution of pneumococcal types, as well as the number of pneumococci present in specimens from individual patients, was similar to the distribution of these organisms in the upper respiratory passages of normal persons.

Beta hemolytic streptococci were isolated from 10 patients, each of whom gave a history of recent contact with cases of streptococcal infection. These streptococci belonged to at least 9 distinct serological varieties. Five different types and 2 strains of as yet unclassified types

TABLE V

Bacteria isolated from 106 patients with primary atypical pneumonia

Pneumococcus		Beta hemolytic streptococcus		*H. influenzae*		Streptococcus MG
Type	Number of patients*	Group Type	Number of patients*	Type	Number of patients	Number of patients
6	7	A 14, 15, 17	1	Could not be identified	34	45
3	6	19, C-94				
29	5	?	2			
9, 11, 16, 18, 20, 23	3					
4, 7, 8, 19, 28, 32, 37	2					
5, 10, 12, 17, 24, 25, 33, 34, 35, 36	1	B, C, H	1			
Total 26	57		10		34	45
Percentage of total patients	53.7		9.4		32.0	42.0

* Number of patients from whom each designated type was isolated.

of group A streptococci were represented. Strains of streptococci belonging to groups B, C, and H were each isolated from individual patients.

Strains of *H. influenzae* were present in cultures from 34 of the 106 patients but in no instance could the organisms isolated be identified by capsular swelling in immune rabbit sera against any of the established types.

B. friedländeri, type A, was isolated from the nasal passages of 1 patient, and *N. catarrhalis* in considerable numbers from 6 patients.

Staphylococci were frequently noted in cultures of the respiratory passages. They showed varying pigmentation and capacity to produce hemolysis on blood agar but only rarely did they appear to be the predominant organism in cultures from the patients in this study.

Colonies of organisms having the characteristics of alpha or gamma streptococci were frequently seen on blood agar plates inoculated with sputum or material from the nasopharynx. Appreciable numbers of organisms in these general categories were seen on blood agar cultures from 33 of the 106 patients. None of the many strains of alpha and gamma streptococci isolated by this method and tested by appropriate serological techniques could be identified as streptococcus MG.

Cultures of the blood from all patients showed no bacterial growth. Cultures of each available specimen of pleural and cerebrospinal fluid remained sterile.

In no instance was evidence obtained which indicated that any one of the bacterial species isolated from these patients by routine methods was causally related to the disease.

A non-hemolytic streptococcus, designated as streptococcus MG, was isolated from sputum or nasopharyngeal cultures of 45 of the 106 patients. In some instances, this streptococcus was cultured directly from the throat or from fresh sputum. It was also cultured, however, from source materials which had been stored at −70° C. for periods varying from a few weeks to more than 1 year. The special techniques for isolating streptococcus MG and the results of studies on this microorganism in primary atypical pneumonia are described in the accompanying paper (22).

VIRUS STUDIES

A continuous effort was made throughout this study to recover from specimens obtained from the patients in this series, as well as from specimens received from similar patients elsewhere, infectious agents other than bacteria which might be etiologically related to primary atypical pneumonia. A large number of specimens obtained from patients with this illness were inoculated in various animal species by several routes and, in many instances, serial passages were carried out. The specimens inoculated included sputa, nasopharyngeal washings, plasma, pleural, and cerebrospinal fluids, and suspensions of consolidated human lung from 9 fatal cases.

The animals used included mice, cotton rats, hooded rats, white rats, and hamsters which were inoculated by the intranasal, intracerebral, intraperitoneal, or subcutaneous route; guinea-pigs which were inoculated intraperitoneally and subcutaneously; rabbits which were inoculated intravenously, intraperitoneally, and subcutaneously; as well as monkeys, cotton rats, and hamsters, which were inoculated intratracheally and intranasally. Chick embryos at various stages of maturation were also inoculated by several techniques, including inoculation into the allantoic, amniotic, or yolk sacs, as well as directly upon the chorioallantoic membrane. Chick-embryo passage materials were inoculated in each of the animal species mentioned above as well as in chimpanzees.

With sputa obtained from certain patients, pulmonary consolidation was repeatedly induced following primary intranasal inoculation in cotton rats. Chick-embryo passage materials were also found to be capable of inducing pulmonary consolidation in either cotton rats or hamsters. Similar consolidations, however, were found to occur in both species following the intranasal inoculation of various control materials. The pulmonary lesions which were noted following inoculation with potentially infective specimens could not be distinguished from those which followed inoculation with control materials, and none of the lesions could be reproduced regularly on serial passage in either species. No evidence was obtained to indicate the presence, in any of the human source materials studied, of a non-bacterial infectious agent capable of producing signs of infection which could be reproduced in series.

Infectious agents, apparently harbored by animals used in these experiments, were encountered repeatedly and seriously complicated attempts to isolate an infectious agent from the human materials. Lymphocytic choriomeningitis virus, the pneumonia virus of mice (25), hereinafter referred to as P.V.M., as well as another latent virus of mice belonging to the psittacosis group of viruses (26), were recovered and identified. It was possible to show in each instance that these agents were derived from the mice used and not from the human materials.

Early in the course of this study, it was observed (27) that cotton rats and rabbits inoculated with certain specimens from patients or with passage materials derived from them developed antibodies capable of neutralizing a heterologous virus, P.V.M., whereas animals inoculated with control materials did not. This evidence was at that time thought to indicate the presence, in these specimens from patients with primary atypical pneumonia, of a virus which possessed minor antigenic components in common with P.V.M.

Subsequent studies have necessitated reinterpretation of the original data. It has been found that in cotton rats and rabbits, as well as in hamsters, the formation of neutralizing antibodies against P.V.M. sometimes could be stimulated by the inoculation of non-infectious materials. Thus it appears that each of these animal species at times and under circumstances not as yet predictable may harbor latent agents which in response to non-specific stimulation induce the formation of specific antibodies against P.V.M. Under these circumstances it is apparent that an antibody response against P.V.M. in any of these species cannot be attributed to specific stimulation by a virus in material of human origin.

SEROLOGICAL STUDIES

Sera obtained from patients with primary atypical pneumonia during the acute and convalescent phases of the illness were tested for the presence of antibodies against a number of viruses known or thought to be capable of inducing acute respiratory disease in human beings. Tests of this nature were carried out upon sera, not only from the 106 patients admitted to the Rockefeller Hospital and described in this study, but also from a number of patients with primary atypical pneumonia treated elsewhere.

The agents used in these tests were influenza A virus, influenza B virus, swine influenza virus, psittacosis virus, and lymphocytic choriomeningitis virus. The results of these tests are shown in Table VI.

With but one exception, no significant increase in specific antibodies against any of these viruses was demonstrable in the serum obtained during convalescence as compared with the serum ob-

TABLE VI

Results of serological tests against certain pneumotropic viruses in patients with primary atypical pneumonia

Virus	Method	Number of patients tested			Results of tests	
		R.I.H.* patients	Outside† patients	Total patients	Significant increase in antibodies. No. of patients	No increase in antibodies. No. of patients
Influenza A	R.B.C.‡ agglutination	47	49	96	1**	95
Influenza B	R.B.C. agglutination	42	47	89	0	89
Swine influenza	R.B.C. agglutination	8	0	8	0	8
Psittacosis	Complement fixation	25	37	62	0	62
Lymphocytic choriomeningitis	Complement fixation	16	12	28	0	28

* R.I.H. patients = Patients studied in the Rockefeller Institute Hospital.
† Outside patients = Patients studied elsewhere.
‡ R.B.C. agglutination = agglutination of chick erythrocytes (Hirst technique).
** R.I.H. patient studied during the 1943–44 influenza A epidemic.

tained from the same patient during the acute phase of illness. A definite antibody response against influenza A virus occurred in the convalescent sera of one patient who had primary atypical pneumonia at the Rockefeller Institute Hospital during the outbreak of influenza A in the winter of 1943–44. The evidence obtained from serological studies strongly suggests that none of the viruses tested was causally related to the illness in the group of patients included in this investigation.

Tests for the presence of antibodies against *Rickettsia diaporica* were not carried out with sera from these patients. However, various specimens obtained from most of the patients were inoculated into susceptible animals and in no instance were rickettsiae recovered. The attempts of others (28) to isolate rickettsiae were unsuccessful also and antibodies against the rickettsia of Q fever were not demonstrable in the sera of any of their patients with primary atypical pneumonia.

In the course of testing sera from the patients in this study for complement-fixing antibodies, a peculiar and unexpected phenomenon was encountered (29). The convalescent sera from 14 of 35 patients tested showed the capacity, not present in acute-phase sera, to fix complement with a variety of apparently unrelated antigens prepared from normal and infected organs of several different species. Similar reactions were not observed in comparable sera from 23 patients with other acute infectious diseases. This phenomenon obviously complicates the interpretation of complement-fixation tests in primary atypical pneumonia. In the light of these observations, it seems necessary to re-evaluate the significance of serological studies in this disease which were dependent upon results obtained with the complement-fixation technique when relatively crude tissue antigens were employed.

Sera from 18 of the patients with primary atypical pneumonia were also tested for the presence of the so-called "C-reactive protein" (30). It will be recalled that notably in pneumococcal pneumonia, but also in other acute infectious diseases, there is present in the serum during the acute phase of illness an abnormal protein which has the peculiar property of reacting with the C or somatic polysaccharide of the pneumococcus. It was found that this protein was present in the acute-phase serum of all but one of the patients with primary atypical pneumonia whose sera were tested, and that it disappeared from their sera during convalescence, as it does in other acute infectious diseases.

Sera obtained from 64 of these patients throughout the course of primary atypical pneumonia were tested for the presence of cold hemagglutinins against human Group 0 erythrocytes (31, 32). It was found that sera of 12, or 18.5 per cent, showed this property.

Reports from other laboratories (31 to 36) have recorded a variable although generally higher incidence of cold hemagglutinins in sera of patients with this disease. The lower percentage of positive reactions and the relatively low titers with sera of patients in this group may be attributable to the method used in collecting some

of the sera, to prolonged storage of certain of the sera before testing, and possibly to the fact that many of the patients in this series were only mildly ill.

Prior to the observation of cold hemagglutinins in this disease, some of the specimens of blood obtained from patients in this series were allowed to clot at 4° C. before the serum was separated. Subsequently, it was found that hemagglutinins present in high titer could be completely absorbed from a specimen of serum by contact with a suspension of human erythrocytes at a temperature of 4° C. It seemed advisable therefore to allow blood specimens to clot at room temperature and to separate the serum prior to refrigeration.

It has been noted previously that in sera obtained from patients with primary atypical pneumonia and stored for long periods of time, the capacity for cold hemagglutination appeared to be less than in sera recently obtained from similar patients (31, 33). One worker (35) retested 20 specimens of serum after storage at 4° C. for periods ranging from 2 to 5 months and found that, in all but 1, the titer of cold agglutinins had diminished. Seven specimens of serum from patients in the present series were likewise tested on 2 occasions with similar results. At the time of the initial tests, the sera had been stored for periods varying from 2 weeks to 6 months but all showed cold agglutination, in dilutions ranging from 1:40 to 1:160. When tested again 10 or 11 months later, 2 sera agglutinated erythrocytes with an undiminished titer of 1–80, 2 agglutinated only in a dilution of 1–10, and 3 had lost completely the property of cold agglutination.

Tests for cold hemagglutination were carried out upon sera of patients in the present series using 2.0 per cent suspensions of erythrocytes as originally recommended. Ten of the 12 patients in this series whose sera contained cold hemagglutinins were ill for periods longer than the average duration of illness for the total group. Other observers have also noted a positive correlation between either the incidence or the titer of cold hemagglutinins and the severity of illness in patients with primary atypical pneumonia (31, 36).

Acute and convalescent sera from each of the 106 patients were tested for the presence of agglutinins against the non-hemolytic streptococcus designated as streptococcus MG (22). It was found that 68, or 64 per cent, of the 106 patients developed in their sera during convalescence agglutinins against this microorganism.

The incidence of positive reactions in agglutination tests with streptococcus MG and serial specimens of serum from these 68 patients (MG positive group) is shown in Figure 1. Although

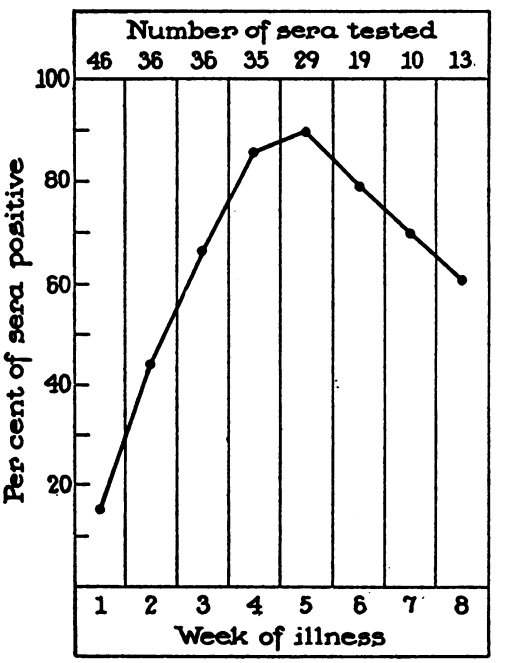

FIG. 1. TIME OF OCCURRENCE OF POSITIVE REACTIONS IN AGGLUTINATION TESTS WITH STREPTOCOCCUS MG AND SERA FROM 68 SELECTED PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA (MG-POSITIVE GROUP)

Each patient in this group developed in his serum during convalescence agglutinins against streptococcus MG. Only one specimen of serum per patient per week was included in this analysis.

positive reactions were noted in 15, 44, and 67 per cent of the sera obtained from these patients during the first, second, and third weeks of illness, respectively, they were found in 86 and 90 per cent of the sera obtained during the fourth and fifth weeks of illness. In 58 (85 per cent) patients, agglutinins were first detected in specimens of serum obtained on the day of defervescence or later in convalescence. In the sera of 10 patients (15 per cent), agglutinins were

noted from 2 to 19 days before defervescence, but the maximum titer of the sera of all but 3 of these patients was not attained until after the temperature had returned to normal. It may be said, therefore, that agglutinins against streptococcus MG are most frequently detectable in sera of patients with primary atypical pneumonia 4 to 5 weeks after the onset of illness and, in most instances, make their first appearance following defervescence.

In view of the frequency with which a serological response against streptococcus MG was observed in these patients, it seemed of interest to determine in what other respects the 68 patients who developed antibodies against this microorganism (MG positive group) could be distinguished from the 38 patients in whose sera such antibodies were not demonstrable (MG-negative group).

On the basis of clinical impressions, the MG-positive group seemed to include patients who were more ill than most patients in the MG-negative group but no satisfactory quantitative criteria except those relative to the duration of the illness could be found for estimating the relative severity of illness in individual patients of the 2 groups. From the standpoint of severity, the symptoms, physical signs, and clinical-laboratory findings of many individual patients in the 2 groups were indistinguishable. The average number of lobes involved was by physical examination 1.64 and 1.39 and by x-ray 2.01 and 1.55 in the MG-positive and MG-negative groups, respectively. On the basis of x-ray evidence, involvement of more than one lobe occurred in 56 per cent of the MG-positive group and in 47 per cent of the MG-negative group. The average and range of the total leukocyte counts, the degree and frequency of E.S.R. acceleration, the distribution of bacteria other than streptococcus MG, and the negative results of serological tests against certain pneumotropic viruses were essentially the same in both groups.

Nevertheless, it was possible to demonstrate certain quantitative differences between patients in the 2 groups taken collectively if data relating to the duration of illness were compared. It was found that the duration of fever, of abnormal physical signs, and of roentgenological evidence of pneumonia, as well as the duration of hospitalization, were considerably longer in the MG-positive group than in the MG-negative group.

Comparable data for the 2 groups are illustrated graphically in Figure 2. Fever persisted

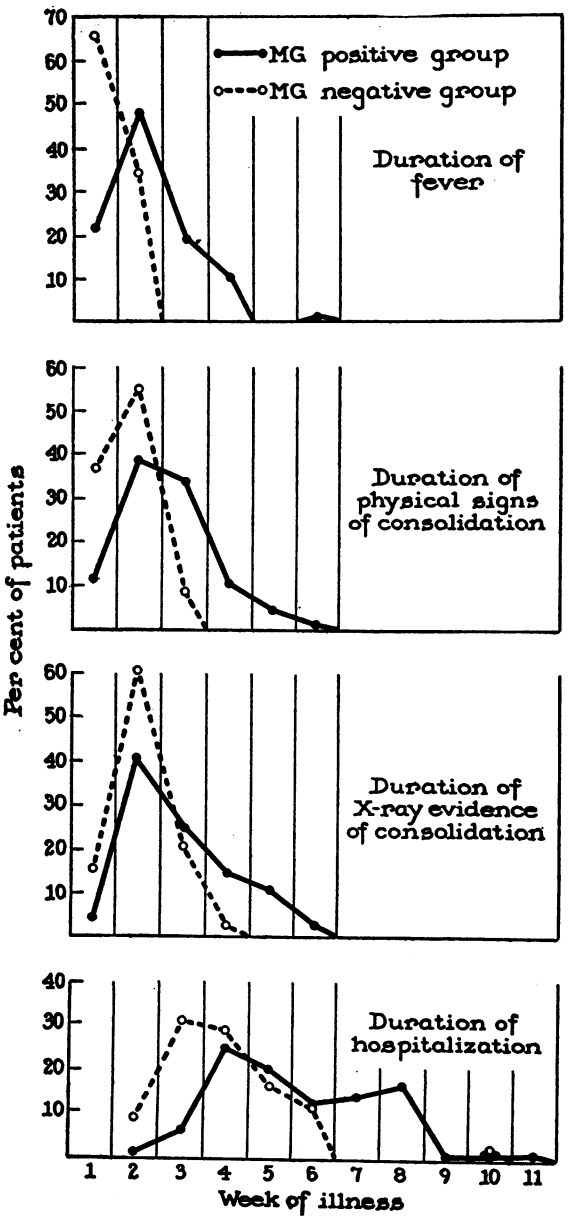

FIG. 2. COMPARISON OF QUANTITATIVE DATA RELATIVE TO THE DURATION OF ILLNESS IN THE MG-POSITIVE AND MG-NEGATIVE GROUPS OF PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA

MG-positive group comprises those patients who developed in their serum agglutinins against streptococcus MG. MG-negative group is composed of those patients in whose serum such agglutinins were not demonstrable.

for more than 2 weeks in 21 patients (30 per cent) of the MG-positive group and in none of the patients in the MG-negative group. Physical signs of pneumonia were present for more than 2 weeks in 34 patients (50 per cent) of the MG-positive group and in only 3 patients (7 per cent) of the MG-negative group. Roentgenological evidence of pneumonia was detectable for more than 3 weeks in 20 patients (29 per cent) of the MG-positive group and in only 1 patient of the MG-negative group. Similarly, 23 patients (34 per cent) of the MG-positive group but only 1 patient of the MG-negative group required hospitalization for more than 6 weeks.

Further analysis revealed that the average duration of illness was longer, not only in the MG-positive group as compared with the MG-negative group, but also within the MG-positive group in direct proportion to the maximum titer of agglutinins against streptococcus MG. This is shown in Table VII. The duration in days of fever, of physical signs of pneumonia, of x-ray evidence of pneumonia, and the period of hospitalization were arbitrarily estimated for each patient from the onset of illness. The average duration in each of these 4 categories was then calculated in groups of patients arranged according to the maximum titer of agglutinins against streptococcus MG observed in their sera throughout the course of illness.

TABLE VII

Relation of duration of illness to the titer of agglutinins against streptococcus MG in the sera of patients with primary atypical pneumonia

Maximum titer of agglutinins against streptococcus MG	Number of patients	Duration of illness			Duration of hospitalization
		Fever	Physical signs of pneumonia	X-ray evidence of pneumonia	
		Average number of days	Average number of days	Average number of days	Average number of days
0	38	6.6	8.9	11.4	26.2
1–10	28	9.4	11.6	14.1	30.5
1–20	20	10.8	14.7	15.8	35.4
1–40 and over	20	17.3	20.4	23.0	46.3
Total group	106	10.1	12.8	14.2	33.0

As shown in Table VII, 38 patients with no demonstrable agglutinins against streptococcus MG had, on the average, fever for 6.6 days, physical signs of pneumonia for 8.9 days, evidence of pneumonia by x-ray for 11.4 days, and hospitalization for 26.2 days. In the groups of patients with maximum agglutinin titers in their sera of 1–10, 1–20, and 1–40 or more, respectively, the average duration of illness was progressively longer in each of the 4 categories mentioned above. Thus, the 20 patients in whose sera the maximum titer of agglutinins (against streptococcus MG) was 1–40 or more the average duration of fever was 17.3 days, signs of pneumonia were present for an average of 20.4 days, and evidence of pneumonia by x-ray for 23 days, while the average period of hospitalization was 46.3 days. It should be pointed out that within the groups of patients divided according to the titer of their sera against streptococcus MG, the duration of illness in individual patients varied over a wide range. Moreover, as might be expected, there was considerable overlapping in the range of the values among the several titer groups. Nevertheless, these observations showed in patients of this series a positive correlation between the duration of illness and the titer of agglutinins against streptococcus MG.

The MG-positive and MG-negative groups of patients also differed markedly with respect to the occurrence in their sera of cold hemagglutinins. The results of serological tests for both cold hemagglutination and agglutination of streptococcus MG are shown in Table VIII.

TABLE VIII

Results of tests for cold hemagglutination and for agglutination of streptococcus MG with sera of patients with primary atypical pneumonia

Cold hemagglutination	Agglutination of streptococcus MG		Total number of patients
	Positive—Number of patients	Negative—Number of patients	
Positive	13	3	16
Negative	19	36	55
Total	32	39	71

Sera from a total of 71 patients, including 64 patients in the present series and 7 patients studied elsewhere,[7] were tested for both types of agglu-

[7] Dr. Warfield T. Longcope of the Johns Hopkins Hospital, Baltimore, Md., kindly provided the specimens of serum from these 7 patients.

tinins. Convalescent sera from 32 of these 71 patients agglutinated streptococcus MG. Of these 32 patients, the sera of 13 also agglutinated human Group 0 erythrocytes in the cold. The sera of 36 patients possessed neither agglutinins against streptococcus MG nor cold hemagglutinins. The sera of 3 patients possessed cold hemagglutinins but not agglutinins against streptococcus MG. Thus it is evident that cold hemagglutinins occurred predominantly but not exclusively in the sera of patients who developed agglutinins against streptococcus MG.

In the 12 patients of the present series whose sera contained cold hemagglutinins, the average duration of fever was 16.4 days, pneumonia was detected by physical signs for an average of 20.2 days, and by x-rays for an average of 20.7 days; the average duration of hospitalization was 44.8 days. It is evident that the average duration of illness in the group of patients with cold hemagglutinins corresponded closely to that observed in the group of patients in whose sera the titer of agglutinins against streptococcus MG was 1–40 or more.

It was pointed out previously that the convalescent sera from 14 of the patients in the present series were capable of fixing complement with a variety of apparently unrelated tissue antigens. All but 1 of the patients in whose sera this property was demonstrated were in the MG-positive group. The sera of five also contained cold hemagglutinins. The average duration of fever in these 14 patients was 13.2 days. Pneumonia was detectable by physical signs for an average of 18.5 days and by x-ray for 17.3 days. The average period of hospitalization was 37.7 days. Thus, the average duration of illness in these patients was considerably longer than the average duration of illness for all the patients and was similar to that observed, not only in patients who had higher titers of agglutinins against streptococcus MG, but also in the group of patients with cold hemagglutinins.

These findings indicate that agglutinins against streptococcus MG, cold hemagglutinins, and the property of non-specific complement-fixation may coexist in specimens of serum from individual patients with primary atypical pneumonia. Moreover they strongly suggest that there is a positive correlation between the incidence of each of these serological properties and the duration of the illness. In the accompanying paper (22), evidence is presented which shows that, despite these similarities, the 3 phenomena are distinct and can be clearly differentiated.

DISCUSSION

During the past 10 years, the illness which has been designated by the term "primary atypical pneumonia" has become a familiar clinical entity which can be recognized on the basis of certain diagnostic criteria. It is possible that this disease may have existed at the time of the last war and even earlier. However, as the validity of diagnosis is dependent upon the careful exclusion of other diseases and to a considerable degree upon the results of roentgenological examinations, there is a limit beyond which retroactive diagnosis becomes merely speculation.

The occurrence of primary atypical pneumonia in certain members of a community in which undifferentiated forms of acute respiratory infection are prevalent has been frequently observed and suggests that this form of pneumonia may be but one manifestation of a widespread respiratory disease. This view is supported by epidemiological observations (37).

In making the diagnosis of primary atypical pneumonia, certain clinical features are particularly helpful. The gradual onset of malaise, cough, headache, and fever, the lack of respiratory distress, the relative bradycardia, the normal leukocyte count, and the paucity of pulmonary signs on physical examination in the presence of x-ray evidence of pneumonia are sufficiently frequent and characteristic findings of this disease syndrome to warrant a presumptive diagnosis.

X-ray evidence of pneumonia may not necessarily be present at the initial examination but usually appears early in the course of illness and clears completely within a few weeks. The x-ray shadow frequently is diffuse and radiates from the hilum but may assume a variety of patterns and, at times, is indistinguishable from that observed in other diseases, particularly other varieties of pneumonia, bronchiectasis, and tuberculosis. The duration of illness should be considered in interpretating x-ray films of the chest in patients with this syndrome and the

rate of clearing is of particular value in excluding a diagnosis of chronic pulmonary disease.

By appropriate techniques, pneumococci can frequently be recovered from patients with the characteristic features of primary atypical pneumonia. It is unusual however to find them in this disease by direct examination of sputum, employing the quellung technique. Moreover, the pneumococcal types isolated are rarely those most frequently associated with lobar pneumonia. It should be pointed out, however, that during the administration of sulfonamide drugs, a considerable reduction in the number of susceptible microorganisms in the nasopharynx and sputum may take place. As a consequence, the presence of certain pathogenic microorganisms, particularly pneumococci or beta hemolytic streptococci, may not be detected. It is therefore important in distinguishing this syndrome from other forms of pneumonia, that the bacteriological examination be carried out whenever possible before sulfonamide therapy is instituted.

The sulfonamide drugs have not been found to be effective in primary atypical pneumonia and are not recommended for treatment. In certain instances, however, it may be impossible to determine whether or not pneumococci or hemolytic streptococci isolated from a patient are implicated in the pathogenesis of the illness. Under such circumstances, an adequate trial of sulfonamide therapy is justified. Prompt defervescence following the administration of a sulfonamide drug may be an indication of effective therapy but may occur also as a coincidence. Consequently, an apparent response to sulfonamide therapy does not necessarily exclude a diagnosis of primary atypical pneumonia.

Early reports on the occurrence of cold hemagglutinins in the sera of patients with primary atypical pneumonia (31 to 33) indicated that this phenomenon might provide a technique useful in diagnosis. It is now apparent, however, that many patients with primary atypical pneumonia do not develop in their sera the capacity to agglutinate erythrocytes in the cold. Furthermore, it has been found that this serological property occurs not only in patients with primary atypical pneumonia but also in an appreciable number of patients with other conditions. Although the significance of the phenomenon has yet to be ascertained, its value as a practical laboratory aid to diagnosis has been disappointing.

Another phenomenon which has been observed with the convalescent sera of certain patients with primary atypical pneumonia is the capacity to fix complement with unrelated tissue antigens (29, 38). This property also does not occur with sufficient frequency to be reliable as a diagnostic technique. Nevertheless, its recognition has served to demonstrate further the frequency with which non-specific reactions occur in the sera of patients with primary atypical pneumonia. It also has made necessary a more critical evaluation of serological data based upon the results of complement-fixation tests in studies of this disease.

It has been pointed out that the clinical picture of primary atypical pneumonia may represent instances of infection by different etiological agents. In certain patients, *Rickettsia diaporica* (11) and the psittacosis group of viruses (12, 13) have been shown to be responsible. These agents, however, have been isolated from or otherwise identified with relatively few cases. In the present series of patients, it was found that neither of these agents had caused the disease and ample evidence is now available to indicate that they were not responsible for the great majority of cases which have been studied during recent years.

The recovery of several infectious agents from patients with primary atypical pneumonia has been reported. A virus obtained by one group of workers (39) appeared to be infectious for mice, guinea pigs, and ferrets, but was lost after a few passages. Others (14) described the recovery of a virus which was infectious for the mongoose, and presented evidence indicating that the agent could be neutralized by the sera of patients convalescent from primary atypical pneumonia. Unfortunately, this species was not available for an attempt to repeat these observations with materials from patients in the present series.

Two viruses recovered from cats have been described in relation to primary atypical pneumonia in man. Epidemiological evidence has been presented (16) to indicate that a few cases

of the human disease in one family might have been related to a respiratory infection of cats which was caused by a virus apparently infectious for this species but not for mice. This agent is different from the other feline virus, recently isolated (40), which has been shown to belong to the psittacosis-lymphogranuloma group of viruses (41).

Certain investigators (15) observed that pulmonary consolidation developed in cotton rats following primary intranasal inoculation of sputum from certain patients with primary atypical pneumonia and presented evidence for the existence of a transmissible agent. Recently (18), these workers have reported the recovery of a filterable agent from certain patients with atypical pneumonia. They also reported that this agent was transmissible in chick embryos and was capable of inducing pulmonary lesions after intranasal inoculation in either cotton rats or hamsters. Moreover, evidence was presented to show that the agent could be neutralized by the convalescent serum but not the acute-phase serum from patients with primary atypical pneumonia. They also reported that pulmonary lesions were induced in both cotton rats and hamsters by the intranasal inoculation of non-infectious materials and that these lesions were similar to those induced by the agent. Furthermore, they found that latent agents present in both species were encountered frequently when serial passages were carried out.

As has been pointed out, the agent previously described in a report from this laboratory (27) was found on further study to be indistinguishable from latent agents antigenically related to the pneumonia virus of mice (25). In the course of the present study, evidence has been obtained which indicates that such latent agents are present in cotton rats, hamsters, and rabbits.

A filterable virus recovered from patients with primary atypical pneumonia (17) was found to be transmissible on intranasal inoculation in young guinea-pigs and cotton rats. The results of neutralization tests with human sera were inconclusive. It was found (18) that guinea-pigs frequently developed lung lesions after intranasal inoculation of broth and one agent was recovered, by intranasal passage in guinea-pigs, which produced pulmonary consolidation in cotton rats and hamsters and resembled an agent obtained from normal hamsters.

The significance of any of these viruses in the pathogenesis of primary atypical pneumonia as observed in the majority of patients remains to be determined.

As reported previously (19), a non-hemolytic streptococcus, isolated originally from the lungs of patients who had died of primary atypical pneumonia, was found to react with the sera of many patients convalescent from this disease. The characteristics of this microorganism, which has been designated streptococcus MG, have been investigated intensively. The results of these studies are presented in separate communications (20, 21). In the accompanying paper (22), studies concerning the relation of streptococcus MG to primary atypical pneumonia are presented in detail and the possible rôle of this microorganism in the pathogenesis of the disease is discussed.

SUMMARY

A comprehensive study of 106 patients with primary atypical pneumonia is presented. The study includes observations on clinical characteristics, roentgenological, electrocardiographic, and clinical-laboratory findings, as well as the results of biochemical, bacteriological, viral, and serological investigations. The observations made upon patients in this series are correlated with the findings reported in other studies on this disease.

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