VIRUS PNEUMONIAS

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UNTIL comparatively recently pneumonias have been classified on a pathologic or anatomic basis, the most common designations having been lobar pneumonia and bronchopneumonia. In the twentieth century, with the isolation and identification of pyogenic bacteria as causative agents, the diagnosis and classification of the pneumonias was further clarified.

The introduction of the sulfonamides and penicillin, which have specific effects on several of the bacterial pneumonias, represented a further forward step. However, the fact that many pneumonias, including those which are now considered to be due to viruses, do not respond to these preparations has raised additional problems. Furthermore, the more frequent use and the improved technics of roentgenograms of the chest have revealed that there are many previously unrecognized types of pneumonia.

Reasons for the lack of interest in pneumonias caused by viruses have been summarized by Reimann:[1] (a) the high incidence in mortality rate of the bacterial pneumonias demanded precedence of interest; (b) the viral infections of the respiratory tract by contrast were of lesser importance; (c) studies were hampered by technical difficulties of research on viruses and a lack of suitable experimental animals; (d) the pulmonary lesions of viral infections are often obscured at necropsy by bacterial invasion, and (e) many pulmonary lesions were undetected because roentgenography in the past was not generally used in mild diseases.

Pneumonias of Known Virus Origin

Measles pneumonia. Pneumonia occurs not infrequently in patients with measles, and roentgenologic and pathologic findings are compatible with those found in other virus pneumonias.

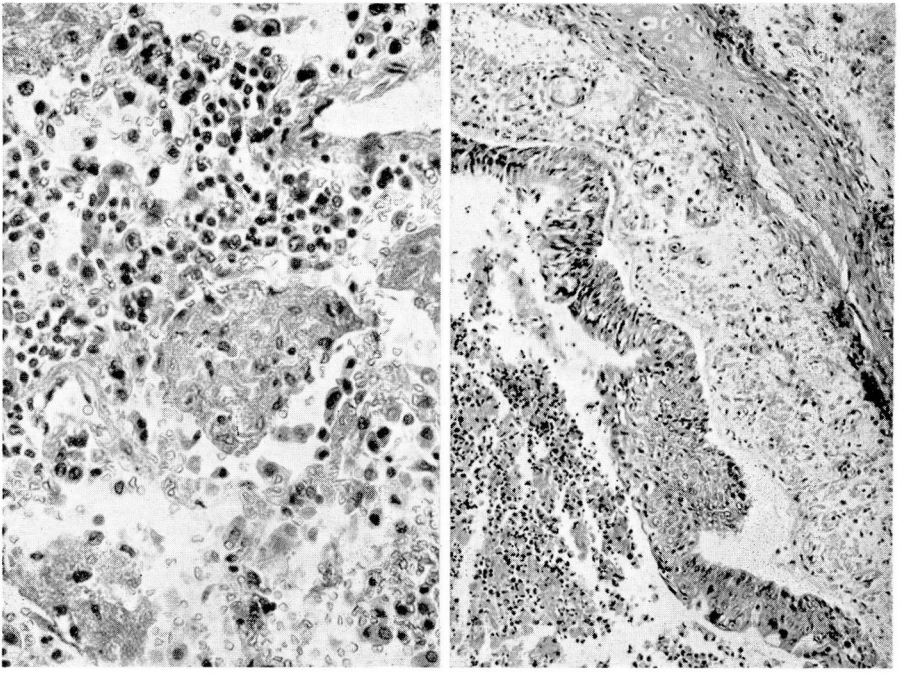
Variola pneumonia. The basis for the pneumonic lesion in patients with variola who develop pneumonia is the underlying infection. This now seems clear, though in the past there was confusion because of the secondary invasion by pyogenic bacteria. Further evidence of the virus causation is offered by the interesting work of Howat and Arnott,[2] who reported a group of patients who developed pneumonia following contact with variola but did not develop variola itself.

Vaccinia pneumonia. Typical virus pneumonia can follow vaccination for smallpox in human beings. Lillie and Armstrong[3] have demonstrated the same reaction in animals.

Varicella pneumonia. Cases of pneumonia associated with chickenpox have been reported.[4,5] Waring *et al.*[6] have described the pathologic picture of virus pneumonia in the autopsy of an adult with chickenpox and pneumonia.

Pneumonia of lymphocytic choriomeningitis. Several authors have reported cases of a typical virus type of pneumonia proved pathologically in patients with lymphocytic choriomeningitis.

Influenzal pneumonia. Influenza has been recurring in pandemics and epidemics for centuries. Secondary invasion by bacteria has caused confusion in spite of the fact that a virus was thought to be the cause of the pandemic of 1918. However, with the discovery of influenza virus A and B, proof has become available of the existence of a true influenzal virus pneumonia. Furthermore, the pathologic picture of pneumonia accompanying endemic and epidemic influenza is not unlike that of other virus pneumonias.



(*a*) (*b*)

FIG. 1. (a) Virus (primary atypical) pneumonia, demonstrating interstitial pneumonitis with mononuclear infiltration (x 200). Death occurred on the fourteenth day of illness. (b) Same case, showing ulceration and squamous hyperplasia of mucous membrane of a bronchiole with dilatation and mononuclear infiltration of its wall (x 70).

It is not known whether the pandemic of 1918 was due to influenza A virus or influenza B or to an as yet unidentified strain. In any event, both A and B influenza occur in endemic form as well as in epidemics. In the recent epidemics they have occurred with the following frequency: influenza A, approximately every two to three years; influenza B, approximately every four to five years. The last major outbreak of influenza B was in 1945, and a mild epidemic of influenza A occurred in the spring of 1947.

A vaccine containing influenza virus A and B has been prepared and used to some extent. It apparently confers specific immunity. However, its use against influenza and its complicating pneumonia in the population at large is not as yet recommended by most authorities because (1) the period of protection may not extend beyond one season, and (2) the disease is now generally mild and of comparatively low incidence and the epidemic is over so rapidly that effective mass immunization cannot be accomplished within one week's time required for the vaccine to become effective. On the other hand, vaccination is generally considered desirable for the protection of elderly or debilitated individuals and for industrial, institutional, and essential public service personnel. The use of the influenza vaccine has proved[7,8,9,10,11] disappointing in several recent instances due to the fact that the epidemics were complicated by previously unrecognized substrains.

Viruses of the psittacosis group. The transmission of virus diseases from birds to man is widely recognized in psittacosis, or parrot fever, which results in a typical pneumonia. Not only may members of the parrot family, which includes canaries and finches, infect man, but so may other species of wild or domesticated birds such as pigeons, doves, and barnyard fowl. The mortality rate from psittacosis has been as high as 40 per cent, especially in older age groups. The diagnosis can be confirmed by complement fixation tests, which the National Institute of Health in Washington, D. C., has cooperated in performing. Some cases have been successfully treated with penicillin.

Pneumonias of Probable Viral Origin

In this group are included (1) pneumonia of infectious mononucleosis, (2) pneumonia of erythema multiforme exudativum, and (3) certain pneumonias of infants. There is growing, although presumptive, evidence that these types of pneumonia are caused by viruses, though as yet the causative agents have not been identified. The roentgenologic and pathologic appearance and the course, however, are similar to the pneumonias of known virus origin.

Other Virus Pneumonias

Primary atypical pneumonia of unknown cause includes a group of pneumonias which has come to occupy an important position in present-day medicine. According to Reimann, there are several reasons for the increased importance: (1) the great reduction in the number of severe bacterial pneumonias by sulfonamide chemotherapy and penicillin, which allowed attention to be given to the milder varieties; (2) their establishment as entities; (3) the more frequent use of roentgenography, and (4) the increase in the number of viral pneumonias in epidemics, particularly among the armed forces during World War II.

The disease, which has come to be called primary atypical pneumonia of unknown etiology and more recently as "virus pneumonia," first came to the attention of the medical profession following a report in 1935 by Major Albert

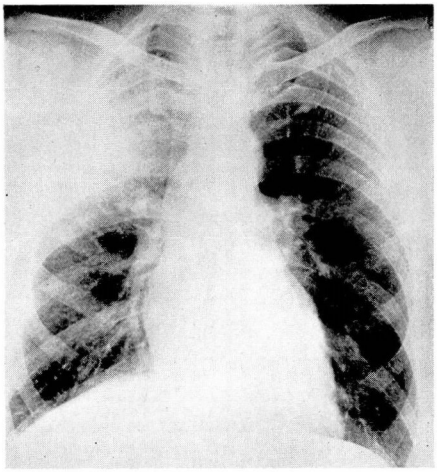


FIG. 2. Case 1. Roentgenogram of chest.

Bowen.[12] He described an epidemic of acute influenzal pneumonitis in several army hospitals in Hawaii. In 1938 Reimann studied similar cases which he grouped into a specific syndrome.

Terminology. Various names have been given to this disease, for example, atypical pneumonia, viral or virus pneumonia, bronchial pneumonia, acute pneumonitis, nonbacterial pneumonia, viroid pneumonia, and sulfonamide-resistant pneumonia. The term "primary atypical pneumonia of unknown cause" is probably in most common use and probably will continue as the accepted term until a specific, consistently demonstrable common agent is found.

Etiology. Presumptive evidence of a causative virus has been presented, but final proof is lacking. Since 1938 a number of agents have been isolated by various investigators, but consistent confirmatory evidence has not been obtained. Examples of such viruses are:

Virus of Stokes *et al.*
Mongoose virus (Wier and Horsfall)
Pneumonia virus of mice (PVM) (Horsfall and Hahn)
Mouse pneumonia virus of Dochez
Guinea pig virus of Rose and Molloy
Cotton rat virus of Eaton
Virus of Rhoads
Virus of Johnson
Cat virus of Howard
Grey lung virus of mice (Andrewes)

The studies of the Commission on Acute Respiratory Disease of the U. S. Army[13] helped to confirm the prevalent belief that primary atypical pneumonia is at least initiated, if not caused, by a filter-passing agent, presumably a virus. These studies also suggested that primary atypical pneumonia is a

severe form of the same infection which is responsible for many of the common mild respiratory illnesses.

Pathology. As in virus pneumonias of known etiology, the histologic picture is fundamentally that of interstitial pneumonitis. In contrast to the inflammatory reaction induced by bacteria, that in primary atypical pneumonia is primarily proliferative. Acute focal bronchiolitis is present with desquamation of the mucosa. Ulceration may be extensive, and squamous metaplasia of the epithelium is often present. The bronchioles are frequently dilated, and their walls are infiltrated chiefly with mononuclear cells. The alveoli may be airless and often contain an exudate of mononuclear clear cells and a few polymorphonuclear cells but not much fibrin. Gross areas of atelectasis and emphysema are often present. (Fig. 1)

Incidence. Military mobilization and other displacements of the population may have increased the incidence since 1941. Virus pneumonias outnumbered all other forms of pneumonia occurring in the armed forces during the war. The disease, as noted by Reimann,[14] " . . . seems to occur in two forms, one consisting of severe, isolated, nonseasonal, sporadic cases, the other, far more common, in epidemic form probably consisting of disease characterized by mild respiratory tract infection, commonly called colds, grippe, viroid, pharyngitis, and influenza and their accompanying severer pneumatic forms."

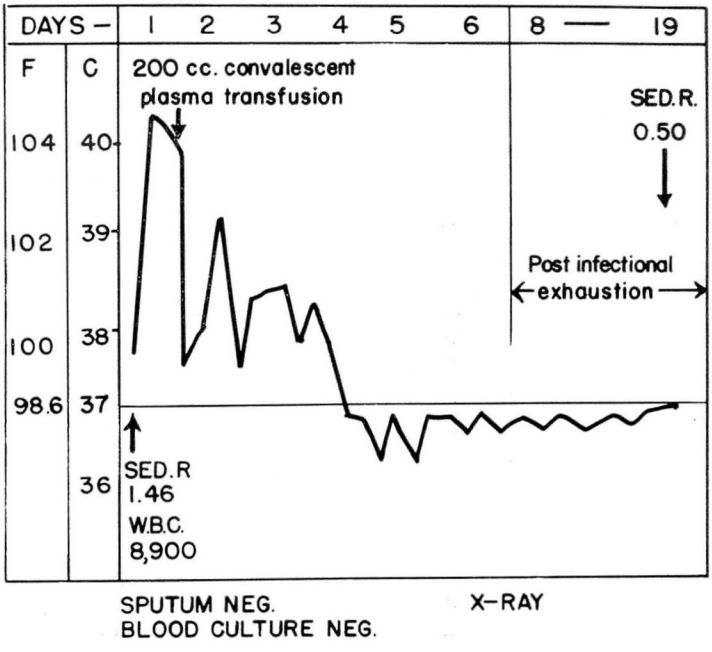


FIG. 3. Case 1. Chart of temperature, laboratory observations, and course.

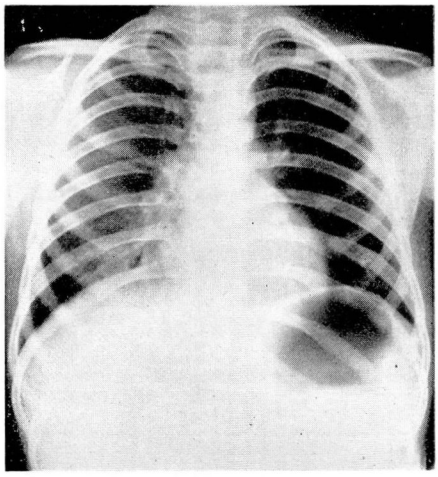


Fig. 4. Case 2. Roentgenogram of chest.

Incubation period. The incubation period is variable. The usual average is believed to be from seventeen to nineteen days with ranges of from one to twenty-six days.

Immunity. Little is known of immunity. Cases of known recurrences have been seen. (We have treated 1 patient with initial illness and two recurrences within a four-year period.) Inasmuch as the exact etiologic agent is not known, however, recurrences may be due to a different agent or strain rather than to the same one.

Clinical features. Primary atypical pneumonia of unknown cause is usually a relatively mild self-limited disease, the onset of which is usually insiduous. Severe respiratory distress is usually absent. The febrile period averages seven to eight days but may last up to forty-five days. There is relative bradycardia, the leukocyte count is normal or only slightly abnormal, and the sedimentation rate is elevated. Characteristic changes may be seen on the roentgenograms. In the diagnosis of pneumonia the x-ray examination is essential; however, the roentgenogram does not demonstrate changes sufficient to distinguish the types of the disease and consequently cannot be relied upon alone to establish the diagnosis of virus pneumonia. The disease does not respond to sulfonamides or antibiotics. Cold hemagglutination occurs late in the course of the disease in about 70 per cent of cases. Agglutination of Streptococcus MG also occurs late in about 70 per cent of cases. The mortality rate is low, estimates generally placing it at about 0.1 per cent.

The onset of the disease is usually less abrupt than that of bacterial pneumonias and the symptoms more varied and with more systemic manifestations. Symptoms in their order of frequency are:

General	
Headache	60-70%
Malaise	60-65%
Chills or chilliness	50-60%
Generalized aches	25-30%
Anorexia	23-30%
Nausea	15-20%
Vomiting	10-15%
Respiratory	
Cough	95-100%
Sputum	80-90%
Sore Throat	23-30%
Pain in chest	10-20%
Dyspnea	5-10%
Epistaxis	5%

Objective findings often parallel symptoms in slowness of appearance and multiplicity.

Fever	95-100%
Nasal congestion	50-60%
Pharyngitis	60-70%
Cervical adenopathy	20-30%
Pulmonary signs	80-90%
Dullness	40-50%
Altered breath sounds	60-70%
Rales	80-90%
Friction rub	5-10%
Fluid	1-2%
Bradycardia	60-70%
Tachycardia	10-20%
Cyanosis	10-15%
Signs referable to the central nervous system	1-2%

Complications. Complications are less common than in bacterial and other virus pneumonias. Their order of relative frequency is:

Bronchiectasis
Pleural effusion
Otitis media
Sinusitis
Thrombophlebitis
Cough fracture
Encephalitis
Lung abscess
Empyema
Pericarditis
Pneumothorax
Massive atelectasis
Hepatitis

In addition to routine differentiation from bacterial pneumonias, other types of virus pneumonia must be considered, such as influenza and psittacosis. Coccidioidomycosis, Q fever, toxoplasmosis, brucellosis, and Loeffler's syndrome must also be eliminated.

Treatment. A specific treatment is not available. Supportive treatment includes bed rest, adequate nourishment and fluids, tepid sponge baths, and cool compresses for the fever, and, especially if delirium is present, cough sedation. Oxygen is indicated for cyanosis. Sodium chloride is administered

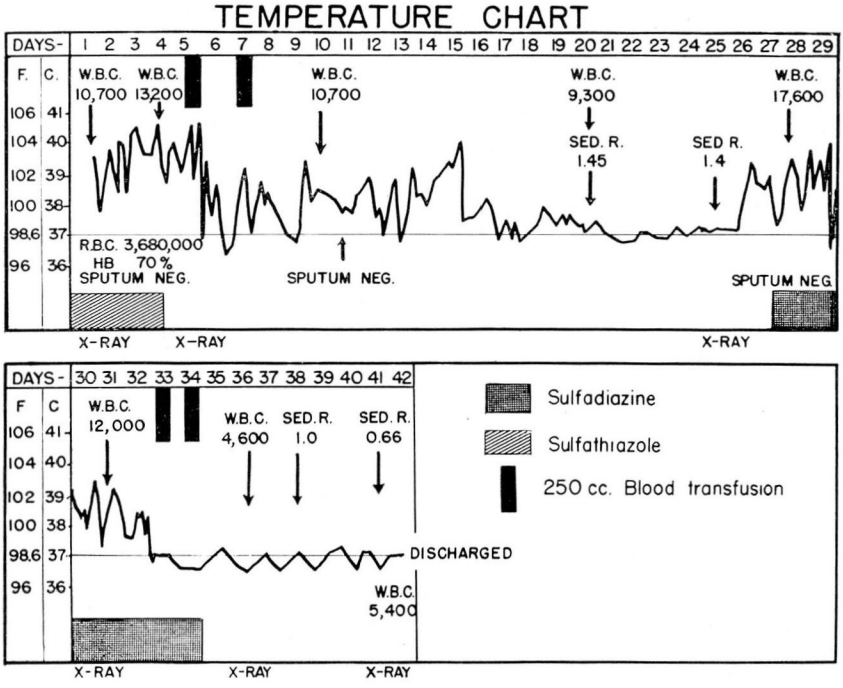


FIG. 5. Case 2. Chart of temperature, laboratory observations, and treatment.

for severe diaphoresis, but antipyretics are generally thought to be contraindicated. Slow resumption of activities in the postinfectional asthenia is required. Sulfonamides or penicillin may be given for bacterial complications or when the diagnosis is uncertain. Convalescent serum has been used. The sedimentation rate is a good guide in convalescence.

Prevention. There are no specific measures of prevention. Avoidance of chilling, fatigue, malnutrition, and exposure to patients having the disease are advisable.

Case Reports

Case 1. A man, aged 41, was admitted to the Cleveland Clinic Hospital after an illness of three days. The onset of symptoms had been gradual, with slight cough and general malaise. The roentgenologic appearance of the pneumonia was essentially of lobar configuration (fig. 2). The clinical characteristics of the illness were, however, those of virus (primary atypical) pneumonia.

The temperature, laboratory observations, and course are shown in fig. 3. A prompt subsidence of the fever and acute symptoms followed the administration of 200 cc. of plasma from a patient convalescing from primary atypical pneumonia. This measure did not, however, prevent a period of postinfectional exhaustion.

Case 2. A boy, aged 11, was admitted to the hospital after sixteen days of fever. Suppression of breath sounds was found over the right middle lung lobe. The roentgenologic examination helped to confirm the diagnosis of pneumonia (fig. 4). Respiratory symptoms did not appear until the third day in the hospital.

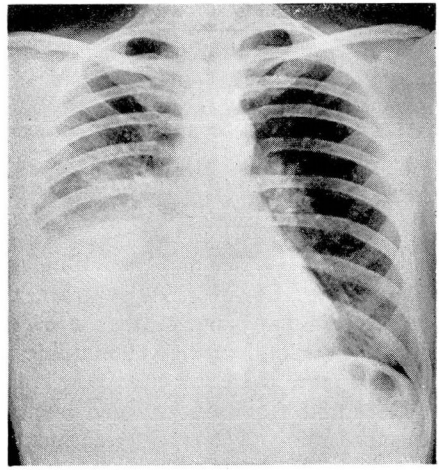


FIG. 6. Case 3. Roentgenogram of chest.

The graphic demonstration of the temperature, laboratory observations, and treatment are shown in fig. 5. The febrile phase of the illness lasted over forty-five days from onset. During this time the physical signs and serial x-ray findings varied considerably in showing shifting areas interpreted as patchy atelectases. The highest titre of the cold agglutinations was 1:560.

Case 3. A housewife, aged 40, had been ill for six days prior to admission with symptoms of alternating chilliness and fever up to 103 F. A nonproductive cough appeared twenty-four hours prior to admission. Roentgenograms of the chest (fig. 6) confirmed the diagnosis of pneumonia in the right lower lung.

The temperature, laboratory findings, and treatment are shown in fig. 7. No response was obtained from penicillin, but dramatic recovery followed the administration of 250 cc. of a standard plasma. The patient was later readmitted, however, with a severe homologous serum jaundice which appeared sixty-two days after the administration of plasma. Recovery from this complication was satisfactory.

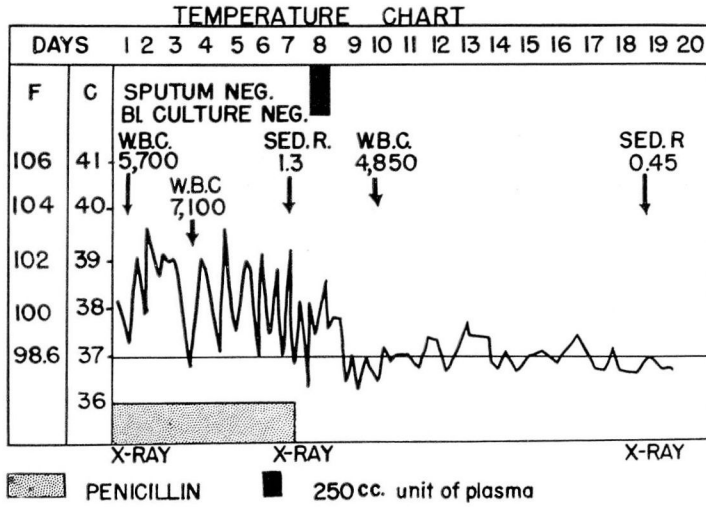


FIG. 7. Case 3. Chart of temperature, laboratory observations, and treatment.

Summary

With the advent of the sulfonamides and penicillin, the frequency of bacterial pneumonias is decreasing; however, in contrast, the incidence of the virus pneumonias is relatively increasing. With the exception of psittacosis, the virus pneumonias do not respond to the sulfonamides or penicillin. Available evidence indicates that more than one virus may be involved in clinically similar pneumonias. Differential diagnosis between bacterial and virus pneumonias is important because the only form of treatment for the virus pneumonias is essentially supportive in nature.

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