Infections

PNEUMONIAS IN ADULTS DUE TO MYCOPLASMA, CHLAMYDIAE, AND VIRUSES

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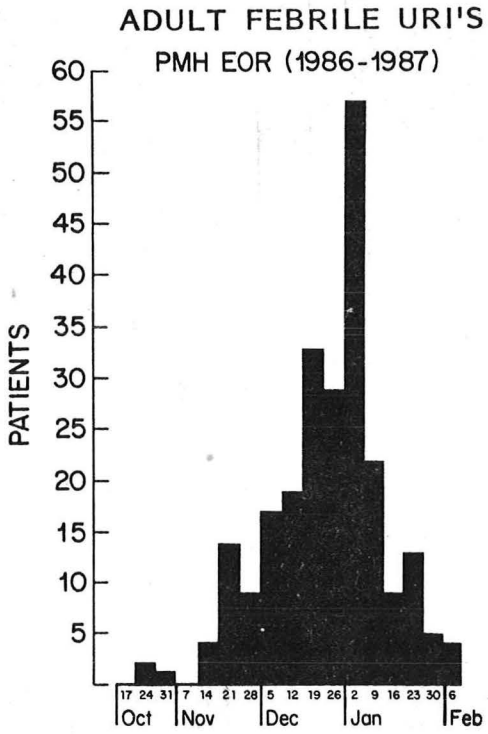

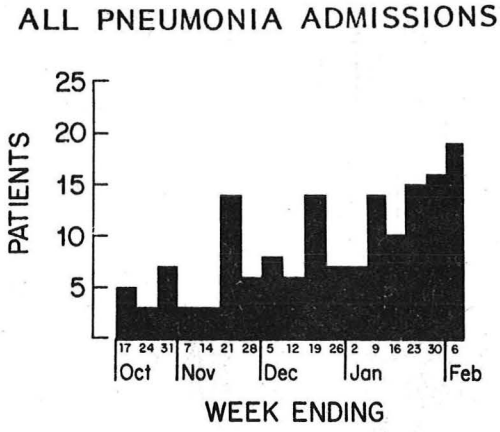

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SCOPE AND NATURE OF THE PROBLEM

Population based studies on the incidence of pneumonia have been infrequently performed. In one such study, during an 8-year interval from December 1, 1963 through November 30, 1971, Foy and her colleagues determined the incidence of pneumonia in a prepaid medical health insurance plan comprised of over 100,000 members in Seattle, Washington (1). They found that total pneumonia rates varied yearly and ranged between 7.2 and 16.8 cases per 1,000 population per year. Only 15% of the cases seen by the physicians caring for this group were hospitalized; 85% of the total number of cases were managed as outpatients. In adults, 35% of all cases of pneumonia were associated with cultural and/or serological evidence of mycoplasma and/or viral infection. Total rates for all cases of pneumonia increased during influenza A2 epidemic years. The highest rates were generally found in the winter quarter, followed by rates occurring during the spring quarter (Figure 1). The major viral and mycoplasma agents

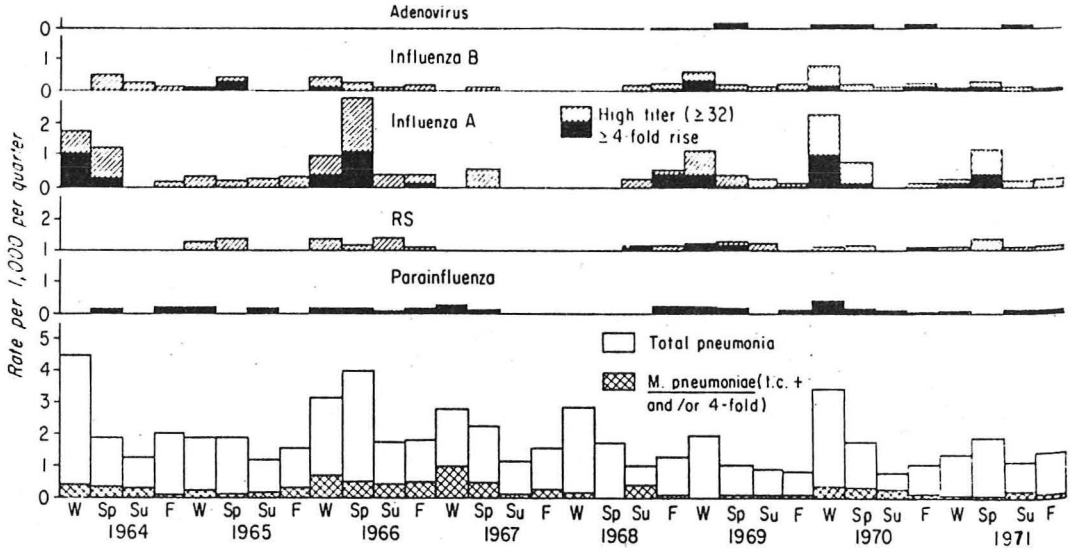

Figure 1. Seasonal rates of pneumonia associated with Mycoplasma pneumoniae and various viruses in adults, Dec. 1, 1963 to Nov. 30, 1971. (Reference 1)

contributing to the etiology of pneumonia in this study were influenza A virus, and Mycoplasma pneumoniae, followed by a smaller number of cases due to adenoviruses, influenza B virus, respiratory syncytial virus (RSV) and parainfluenza viruses. Most of the parainfluenza virus infections were caused by types 2 and 3, but no attempt was made to ascertain the exact contribution of specific agents involved because of antigenic overlap in the complement fixation test. It was recognized that the majority of pneumonias associated with influenza A were related to bacterial suprainfection. Rates for all pneumonia were highest in young children, followed by a peak in pneumonia due to Mycoplasma pneumoniae in the 30-40 year age group.

Pneumonia due to influenza A virus increased in incidence above the age of 60 years. Of interest is their finding that sometimes pneumonia was associated with laboratory evidence of infection to more than one respiratory nonbacterial agent. The severity of disease did not appear different in patients with a single infection as opposed to those with multiple infections as measured by duration of illness and hospitalization rates. In individual reports, however, it has been suggested that in certain individuals, multiple infections can sometimes lead to a more severe course than would have predicted by infection with a single agent (2). Overall rates for pneumonia as determined in this study were similar to that observed in the National Health Survey.

In Houston, Texas, during the years 1975-1978, adult hospitalizations for pneumonia sharply increased during influenza A epidemics but did not change much during influenza B epidemics, a finding that was also seen in the Seattle study (Figure 2.) (3). Although hospitalizations for pneumonia did

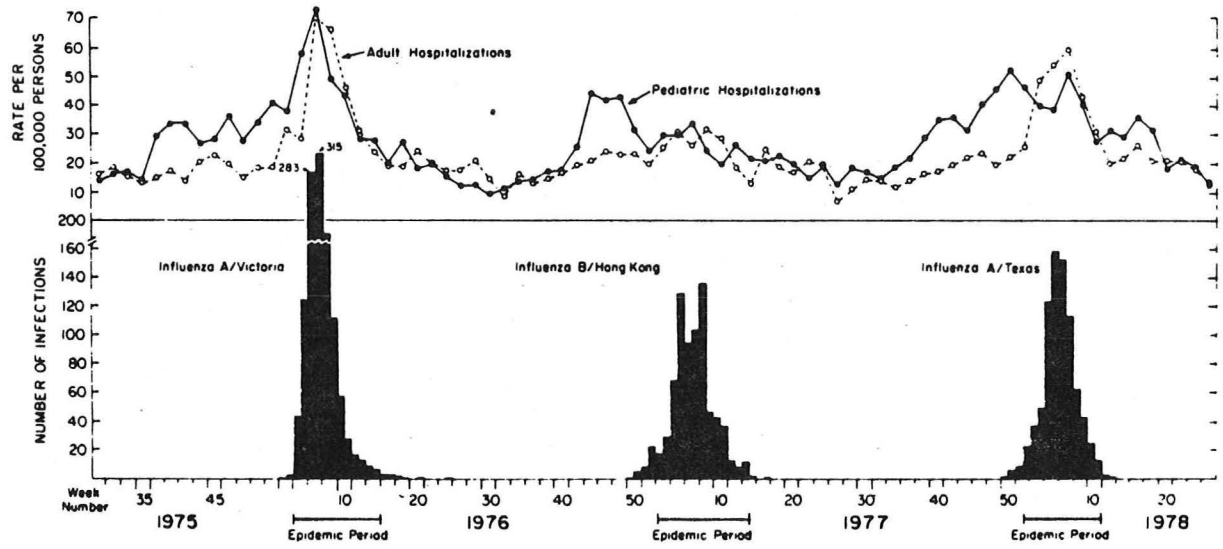

Figure 2. Pediatric (<15 years of age) and adult hospitalization rates for acute respiratory disease by two-week periods estimated for Harris County, Texas (top), and the temporal relation to influenza virus epidemics defined by virologic surveillance at the Influenza Research Center, Houston (bottom), 1975-1978.

not increase in Houston during the 1976-1977 influenza B epidemic, an increased number of cases hospitalized with complications due to influenza B virus infection was seen in Dallas, Texas at this time (4). The etiology of community acquired pneumonia in 54 adult, outpatients in Sweden has been determined (5). Using rises in antibody titer between acute and convalescent sera to determine etiology, these investigators found evidence of Mycoplasma pneumoniae infection in 37%, Streptococcus pneumoniae in 9%, Hemophilus influenzae in 12% (6% Type B and 6% nontypeable), influenza A virus in 6%, Chlamydia psitacci in 4% and influenza B virus, parainfluenza 3 virus, respiratory syncytial virus and adenovirus in 2% apiece. Multiple infections occurred in several patients and there was no serological evidence of infection with a particular microorganism in 41%.

The etiologic agents of community acquired pneumonia in adult patients hospitalized for their disease can be examined (Table 1). Six recent studies

Table 1

Etiologic Agents of Community Acquired Pneumonia in Hospitalized Adult Patients

Etiologic Agent	Number of Patients*					
Streptococcus pneumoniae	79	69	40		96	18
Staphylococcus aureus	11	1	3		3	2
Hemophilus influenzae	4	5	5		4	8
Klebsiella pneumoniae	9					1
Legionella pneumophila		1	1		19	
Other gram negative	5		1		1	2
Anaerobes	3					
Total bacterial	111	75	54	40	122	31
Mycoplasma pneumoniae	7	18			3	7
Influenza A	9	15	4	5	7	
Influenza B		1	1	6		4
Adenovirus				12	1	
Respiratory syncytial virus	1	3			2	
Parainfluenza	3	1		21		3
Varicella		2			1	
Chlamydia psittaci		3			7	
Total nonbacterial	20	45	5	27	21	14
Nonbacterial alone	12	21	1		13	4
Mixed nonbacterial & bacterial	8	24	4	43	8	10
Etiology undetermined	25	27	29		3	37
Total patients studied	148	127	80	110	127	81
Location of study	Wisconsin	Sweden	England	Romania	England	So. Africa
Study interval	1969-70	not given	1979-82	1984	1980-81	1980
Reference	6	7	8	9	10	11

* The number of patients in each column may not add up to the total patients studied because some had multiple etiologies.

were selected for analysis because they reflected a world-wide authorship and because an attempt had been made to estimate the contribution made by both bacterial and non-bacterial agents (6-11). Bacterial etiologies contributed most significantly to the problem of community acquired pneumonia in adult hospitalized patients. The most frequent microorganisms were Streptococcus pneumoniae followed by Staphylococcus aureus, Haemophilus influenzae, Legionella pneumophila, and other gram-negative bacteria. The role of anaerobic bacteria in the etiology of pneumonia was not systematically studied in five of the series. One study accentuating the role of Legionella pneumophila in the etiology of pneumonia was from Nottingham, England and showed the propensity of this microorganism to be associated with specific geographical sites. The major non-bacterial agents implicated in these studies included Mycoplasma pneumoniae, influenza A and B viruses, adenoviruses, RSV, parainfluenza viruses, varicella and Chlamydia psittaci. All of these latter agents could be seen as single pathogens but influenza A and B viruses, adenoviruses, RSV, parainfluenza viruses and varicella virus were also seen associated with bacterial pneumonia. Non-bacterial agents contributed from 6-35% to the etiologies of all cases. An indication of

the approximate incidence of nonbacterial pneumonia without bacterial suprainfection can be ascertained in five of the series and ranged from 1-17% of the cases. The association of influenza A and B viruses, rubeola virus and varicella virus with bacterial suprainfection has been well established. Recently, bacterial suprainfection has been shown to occur in adults who have evidence of infection with adenoviruses and RSV. The frequency of bacterial suprainfection in association with Mycoplasma pneumoniae infections is difficult to ascertain. It has been considered that bacterial suprainfection of Mycoplasma pneumoniae pneumonia was an infrequent if not rare occurrence. Pneumococcal bacteremia, for example, occurring in the course of mycoplasma infections must be extremely uncommon. However, serological evidence of infection with Streptococcus pneumoniae and Hemophilus influenzae can occur concomitantly with antibody titer rises to Mycoplasma pneumoniae. One case of staphylococcal pneumonia was associated in the Wisconsin series with Mycoplasma pneumoniae seroconversion. Whether Mycoplasma pneumoniae infection predisposes the host to bacterial suprainfection or whether the two events occurred together by chance remains to be determined. A relatively large number of pneumonias have an undetermined etiology and this varies between series of patients. In most instances, these pneumonias appear to respond to penicillin therapy, a phenomenon of interest in suggesting their possible etiologies.

PRIMARY ATYPICAL PNEUMONIA

The concept of primary atypical pneumonia was set forth in a landmark article by Hobart A. Reimann in 1938 (12). The major bacteria causing pneumonia were known at that time with the exception of Legionella pneumophila. The clinical entity of psittacosis had been elucidated. Influenza A virus had been grown in ferrets by Laidlaw, Andrews and Smith. Reimann described 8 cases of what he called atypical pneumonia, which he thought was due to a filterable virus. The description of cases allow a view of untreated primary atypical pneumonia. In most of his cases, it now seems probable that Mycoplasma pneumoniae was the etiologic agent. The illness oftentimes began insidiously with fever, headache and pharyngitis. With descent of the disease process into the respiratory tract, the larynx became involved and hoarseness was present. Finally, laryngotracheobronchitis and pneumonia occurred. A cough developed that was troublesome to the patient, could not be alleviated and was only slightly productive. In some patients, a pulse-temperature dissociation occurred. During the course of the disease, which oftentimes lasted several weeks, patients became dyspneic and cyanotic. Two of the patients became delirious and had central nervous system dysfunction during the course of the infection. On physical examination, the patient was flushed, and had evidence of pharyngitis. The physical examination of the chest usually revealed scattered rales without striking evidence of consolidation; in one patient a large pleural effusion was present. The white blood count was only modestly elevated. Chest x-rays revealed mottled or diffuse areas of infiltration. Attempts to isolate pathogenic bacteria and influenza A virus were unsuccessful in trying to establish an etiology for this syndrome. Reimann, himself, considered diagnoses such as typhoid, psittacosis and epidemic influenza, but the history in none of these cases was consistent and influenza virus could not be recovered. To summarize in his own words, "The infection occurred in adults and began as a mild infection of the respiratory tract; this was

followed by severe diffuse atypical pneumonia and in two cases by the symptoms of encephalitis. Dyspnea, cyanosis, hoarseness, cough without sputum, drowsiness, and profuse sweating were the chief characteristics. The disease lasted several weeks."

In 1943, Finland found elevated cold agglutinin titers in cases of atypical pneumonia. Eaton later isolated the agent in embryonated eggs and Chanock and colleagues were able to grow it on defined media and demonstrate it to be a mycoplasma. The entity of primary atypical pneumonia became well known and later, was defined as pneumonia that did not clear with penicillin or sulfonamides or nonbacterial pneumonia or pneumonia with no sputum or a mucoid sputum without a predominant organism on Gram stain. We recognize today that the clinical entity of primary atypical pneumonia has multiple etiologies, particularly Mycoplasma pneumoniae but also Chlamydia psittaci, the TWAR strain of Chlamydia psittaci, Chlamydia trachomatis, Q-fever, and viruses like adenoviruses, RSV, influenza viruses and parainfluenza viruses. Legionella pneumophila infections are oftentimes considered in the differential diagnosis as well as early bacterial bronchopneumonia (13). In pertinent geographical areas, acute histoplasmosis and coccidioidomycosis can present like primary atypical pneumonia. Major attempts to identify the etiologic agent on clinical grounds have been made but the exact diagnosis usually depends on laboratory determination of the offending agent.

In one study of 150 patients that included all ages, 50 with viral pneumonia, 50 with mycoplasma pneumonia and 50 with bacteremic pneumococcal pneumonia were compared (14). The best discriminating variables were the C-reactive protein determination, the presence or absence of predisposing disease or previous antibiotic treatment, the erythrocyte sedimentation rate, the presence of lymphocytosis and the band neutrophile count. Signs of an upper respiratory tract infection and the presence or absence of auscultatory abnormalities also aided significantly in the discrimination. Determinations favoring bacteremic pneumococcal pneumonia included predisposing disease, a short duration of illness before hospitalization, alcoholism, the absence of signs of an upper respiratory tract infection, high C-reactive protein determinations and erythrocyte sedimentation rates, no prior antibiotic treatment, total leukocyte counts exceeding 15,000, relative lymphocyte counts less than 35%, relative band neutrophile counts greater than 20%, abnormal auscultatory findings and the presence of labor consolidation on chest x-ray. Differentiation between viral and mycoplasma pneumonia could not easily be made. However, symptoms of mycoplasma pneumonia before hospitalization lasted a longer time and these patients were more likely to have received antibiotic treatment in the interval before hospitalization. Patients with mycoplasma pneumonia were more likely to have lobar consolidation on chest x-ray than those with viral pneumonia but in this study, no distinction could be made between mycoplasma pneumonia and bacteremic pneumococcal pneumonia on the basis of roentgenographic findings alone.

In another study comparing community acquired pneumonias, mycoplasma pneumonia tended to occur at an earlier age than Legionnaire's disease, pneumococcal pneumonia or psittacosis (15). Homogeneous shadowing on chest x-ray was more common in Legionnaire's disease and pneumococcal pneumonia than mycoplasma pneumonia. Pleural effusions were uncommon in all groups but occurred most commonly in bacteremic pneumococcal pneumonia as did multilobe

disease on presentation. Hilar lymphadenopathy occurred only in mycoplasma pneumonia. Roentgenographic resolution was fastest in mycoplasma pneumonia, intermediate in psittacosis and non-bacteremic pneumococcal pneumonia, and slowest in Legionnaire's disease and bacteremic pneumococcal pneumonia. Deterioration on chest x-ray after hospital admission characterized Legionnaire's disease and bacteremic pneumococcal pneumonia.

Since the differential diagnosis of primary atypical pneumonia includes pneumonia due to Mycoplasma pneumoniae, chlamydial species, Q fever, adenoviruses, RSV, influenza viruses, parainfluenza viruses, as well as Legionella pneumophila infections and early bacterial pneumonia, therapy should include an antibiotic to which the majority of these microorganisms are susceptible. Chlamydial species are more susceptible to tetracycline than erythromycin. Tetracycline is effective against rickettsiae but not for Legionella pneumophila infections. Approximately 4% of pneumococcal isolates are resistant to tetracycline. A reasonable antibiotic choice is erythromycin at an equivalent dose of 2 grams of erythromycin base per day for 10-14 days. If Legionnaire's disease is diagnosed, a higher dose of erythromycin may be necessary. If a chlamydial or rickettsial etiology is recognized, tetracycline at a dose of 2 grams per day should be given. Occasionally patients with proven Mycoplasma pneumoniae have been treated with erythromycin, failed to respond to therapy, but subsequently responded to a course of tetracycline therapy (16). Conversely, some patients with Mycoplasma pneumoniae infections have responded to erythromycin after a suboptimal response to tetracycline therapy. Viruses may cause primary atypical pneumonia; however, antibiotic treatment in these instances is useless, does not prevent suprainfection, and may actually change the nature of the bacterial species suprainfecting the patient. Antibiotic therapy seems reasonable in this syndrome, however, because it is usually impossible clinically to differentiate between mycoplasma pneumonia and an entity like adenovirus pneumonia in the adult. Advances in rapid laboratory diagnosis may be able in the future to influence treatment options but these techniques are still under development, are expensive and not widely available.

PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE

Mycoplasmas, the smallest free-living microorganisms, are cell wall deficient, but have no relationship to cell wall deficient bacteria with which they were once confused. Mycoplasma pneumoniae attaches to the mucosal epithelium of the respiratory tract via a specific protein which enables the microorganism to adhere to neuraminic acid residues on respiratory epithelial cells. If mycoplasmas cannot attach, there is no damage to the host. Once adherence has occurred, mycoplasmas are able to generate hydrogen peroxide and superoxide anion, resulting in injury to epithelial cells. Since infection occurs commonly in children less than 5 years of age, but disease is rare at this time of life, mycoplasmas may induce disease primarily by immunopathological mechanisms (17,18). In experimental animals not primed by prior mycoplasma exposure, inflammatory changes occur only after a long interval. With reinfection, inflammatory changes occur more briskly. The extrapulmonic manifestations of mycoplasma infection have never been completely explained, but there are reports demonstrating Mycoplasma pneumoniae in sites like cerebrospinal fluid and blood (19). Alternatively, immunopathological reactions may be the primary mechanism involved.

Pathologically, the disease in man is characterized by tracheobronchial, bronchiolar and septal lymphoplasmocytic infiltrates, luminal exudates rich in polymorphonuclear leukocytes, bronchiolar and alveolar cell metaplasia and occasionally diffuse alveolar injury (20). The bronchiole appears to be the major site of attack.

The microorganisms colonize the nasopharynx and transmission of infection occurs only by close contact. Especially conducive to the transmission of Mycoplasma pneumoniae are situations where persons are housed in closed quarters, like military platoon barracks or family unit dwellings. In families, there is a high attack rate and cases continue to occur over a 3-4 month interval (21,22). The cumulative attack rate of mycoplasma infections in families may approach 90% (Figure 3) (21). Mycoplasma carriage

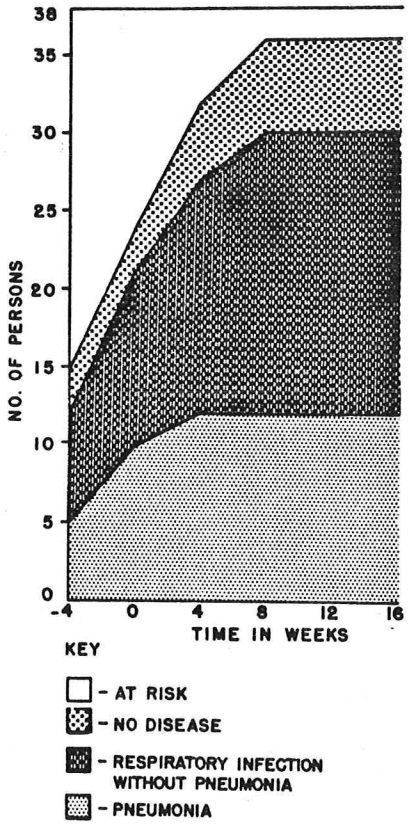

Figure 3. Cumulative incidence of M. pneumoniae infection and clinical response in 38 family members exposed. (Reference 21)

is not affected by antibiotic therapy allowing the family epidemic to continue. Mycoplasma disease occurs throughout the year but is particularly frequent during fall and winter. Increased numbers of cases occur with a 3-5 year periodicity.

Although pneumonia may occur soon after infection, the disease is usually manifested as an upper respiratory tract infection progressively descending into the lung. Pharyngitis progresses into laryngitis followed by tracheobronchitis and finally pneumonia. Hoarseness and dysphonia may be present. Middle ear involvement may occur with bullous myringitis, which

usually heals without scarring. Occasionally, the otitis may lead to tympanic membrane performation. Sinus involvement is frequent but usually asymptomatic. The cough is often intractable and usually only slightly productive of a mucoid sputum which contains mainly polymorphonuclear leukocytes but no predominant bacterial microorganism on Gram stain. When pneumonia develops, the patient has an elevated temperature and sometimes a temperature-pulse dissociation. Headache, irritation, a flushed facies, myalgias and arthralgias are common (23-25). On physical examination, the patient is febrile, appears flushed and usually has physical evidence of pharyngitis. Hemorrhagic bullous myringitis may be present in up to 5% of cases. Physical findings on chest examination usually are limited to scattered rales, wheezes and rhonchi and are often localized to the lung bases. Evidence of consolidation is not striking although Mycoplasma pneumoniae infections can cause lobar pneumonia (26). The white count is usually elevated with a shift to the left, but rarely exceeds 15,000 white blood cells per cubic milimeter and the neutrophile band count is usually less than 10% (14).

Chest x-ray reveals peribronchial infiltrates with accentuation of interstitial markings in adjacent lung segments, patchy alveolar infiltrates usually localized to the lower lobes, especially on the left, and occasionally hilar lymphadenopathy (27). More than one lobe may be involved and a confluent lobar infiltrate may be present in some patients. Less commonly, there is a diffuse interstitial infiltrate and rarely an x-ray picture indistinguishable from the adult respiratory distress syndrome (28,29). Without therapy, the disease course usually lasts approximately 3 weeks, but may extend up to 7 weeks (12). Extrapulmonic manifestations of mycoplasma infection often are a clue to the diagnosis and include bullous myringitis, neurological disturbances suggesting encephalitis or aseptic meningitis and rarely transverse myelitis, arthritis, myopericarditis, hepatic dysfunction, splenomegaly, and skin eruptions (30). A Stevens-Johnson syndrome may occur. Japanese workers have described typical cases of pityriasis rosea which followed mycoplasma infection (32). The cerebrospinal fluid (CSF) may be abnormal with an increased number of cells and an elevated protein concentration. Hemolytic anemia may be present resulting from antibody directed against the I antigen on the red cell membrane (31). Almost all patients recover completely after mycoplasma infection but cigarette smokers may have prolonged abnormalities in diffusion capacity (33). Individual case reports have described pulmonary fibrosis, bronchiolitis obliterans and bronchiectasis following mycoplasma pneumonia (34-36). Glomerulonephritis with continuing renal dysfunction also has been reported (37-38).

The diagnosis is established by culture of the microorganism, or the demonstration of a four-fold rise in antibody by complement fixation or other serological test. A single high complement fixation test antibody titer ($\geq$ 1:128) may be used as presumptive evidence of infection. Cold agglutinin antibody titers at low-level are non-specific but very high values ($\geq$ 1:128) can also be used to support the diagnosis.

Treatment consists of the administration of either erythromycin or tetracycline as outlined in the therapy of primary atypical pneumonia. The patient usually responds but it should be remembered that there are reports of inadequate resolution of the disease and the necessity to switch to the

alternate drug to achieve more rapid clinical improvement. Antibiotic therapy does not eliminate the carrier state. Immunity is relatively short-lasting and documented episodes of repeated mycoplasma infection have been reported. A vaccine against Mycoplasma pneumoniae, given present priorities, appears only a hopeful future development.

Illustrative Case - Mycoplasma pneumonia

The patient was an 18 year old man who was well until 8 days prior to admission into the hospital when he developed fever, a sore throat and a nonproductive cough. His oral temperature reached 40°C. Headache developed that had a "pounding" character. The cough persisted and became productive of a mucoid sputum. Oral penicillin was prescribed but did not alleviate his symptoms. Physical examination on admission into the hospital revealed a young man who was confused about time and uncertain about recent events. The oral temperature was 38.8°C and the pulse rate was 100. The pharynx was described as normal. Chest exam revealed harsh breath sounds with bilateral inspiratory rales, especially on the right, anteriorly and inferiorly. There was no egophony or decreased fremitus. Rhonchi were present more on the right than left. Hepatosplenomegaly was present. Laboratory examination revealed 12,200 white blood cells with 70% polymorphonuclear cells, 28% lymphocytes, 1 monocyte and 1 eosinophile. The serum aspartate aminotransferase was 140 (normal < 40). Arterial blood gases on room air showed a pH of 7.55, pCO_2 of 29 and pO_2 of 45. A lumbar puncture was performed which showed 31 white blood cells, 95% of which were mononuclear cells. The cerebrospinal glucose was 69 mg/dl and the simultaneous plasma glucose 155 mg/dl. The patient was treated initially with intravenous penicillin for presumed pneumococcal pneumonia and partially treated bacterial meningitis. His condition deteriorated but finally he was placed on erythromycin therapy at the advice of a consultant. Mycoplasma complement fixation test titers rose from < 1:8 to 1:64.

Comment: Encephalitis, hepatosplenomegaly, mild hepatic dysfunction were the extrapulmonic manifestations of mycoplasma disease. Typical of mycoplasma pneumonia were the long interval before admission into the hospital, prior antibiotic administration, presence of a sore throat, physical examination of the chest and characteristics of the sputum.

PNEUMONIA DUE TO CHLAMYDIAE

Psittacosis was first described by Ritter in Switzerland in 1879 as a disease of the lungs in patients in contact with sick psittacine birds. Later, in 1929-30, a pandemic of psittacosis occurred involving psittacine birds exported from South America. The clinical manifestations were fully described at that time, the epidemiology was established and this led to control measures which have kept psittacosis or the better, more inclusive term, ornithosis, at a low level of occurrence. Occasionally migrant birds can carry Chlamydia psittaci and persons dealing with them may develop ornithosis. More importantly now, ornithosis is an occupational hazard to the farmer who manages poultry, like ducks and turkeys (17,18,40,41). Clinically, patients with ornithosis have headache, fever, pulse-temperature dissociation, pneumonia, hepatic function abnormalities and hepatosplenomegaly. Intra-alveolar inflammatory changes predominate in ornithosis

with interstitial changes being secondary and less prominent. The chest x-ray reflects this and lobar consolidation may be seen. When lung involvement is minor, the disease can be diagnostically confusing and present as a fever of undetermined origin. Granuloma formation can be found in both the liver and the bone marrow and may be a diagnostic clue. Ornithosis can be diagnosed by serological tests with a chlamydial common group antigen either by complement fixation or the enzyme-linked immunoabsorbent assay (EIA). Treatment is with tetracycline for 10-14 days.

Chlamydia trachomatis can cause an afebrile pneumonia-like syndrome in young infants beginning at the age of 1-3 months and characterized by an afebrile state, failure to gain weight, and a staccato-like cough. On examination, there are rales, expiratory wheezing and evidence of hyperaeration of the lungs. Chest x-ray usually reveals diffuse interstitial pneumonia and hyperaerated lung fields. Laboratory determinations show a modest eosinophilia and hyperglobulinemia. Once so identified, the infants can be treated with oral erythromycin syrup for 3 weeks with benefit. Recently, Chlamydia trachomatis has been isolated from the lower respiratory tract of immunosuppressed patients with pneumonia although four of the six patients reported and the only ones tested did not show a serological response to that microorganism (42). Cases of community-acquired pneumonia in normal adults have also been reported with serological evidence of infection with Chlamydia trachomatis (43). Fifty-two patients were studied and seven were found to have definite or suggestive serological evidence of infection. The seven ranged in age from 22 to 77. The chest x-rays of these cases have been analyzed and the infiltrates were found to be patchy and characteristically streaky with areas of plate atelectasis. There was no particular localization to a single lobe and three patients had radiographic evidence of multilobar involvement (44). Further studies need to be done to corroborate these reports and determine the frequency with which lung involvement occurs.

In Finland, an epidemic of mild pneumonia has been related to a newly described strain of Chlamydia psittaci, capable of being passaged from human to human. This epidemic occurred in adolescents and young adults and had a point prevalence of pneumonia of 15-19 caes per 1000 students at a time of an x-ray survey (45). The contribution of this particular strain of Chlamydia psittaci designated the TWAR strain from TW-183 and AR-39, the first two isolates, has been best examined during a 2½-year study at the University of Washington where infected students presented usually with a mild pneumonia that simulated mycoplasma infection and was often associated with pharyngitis and laryngitis (46). In this study, the TWAR strain of Chlamydia psittaci caused 12% of the pneumonias in the student population. The TWAR strain of Chlamydia psittaci was isolated from the students and serial sera showed conversion to the common chlamydial group antigen by complement fixation tests. Microimmunofluorescence tests revealed specific reactions to the TWAR strain of Chlamydia psittaci. The microorganism isolated from the students formed typical inclusion bodies in tissue culture, were not stained by iodine and were considered typical of Chlamydia psittaci. The clustering of cases had an epidemiology which suggested human to human transmission. Bird-to-human transmission could not be demonstrated in any of the cases. Treatment with tetracycline shortened the course but sometimes, patients did not respond to one gram of erythromycin given for 5-10 days.

This new strain of Chlamydia psittaci was both isolated from the patients and serological reactions to specific antigens were demonstrated. The evidence linking Chlamydia trachomatis to lung disease has either been by isolation alone or just by serological testing. Further studies similar to the Seattle one need to be performed to link Chlamydia trachomatis to lung disease. It is clear, however, that a new strain of Chlamydia psittaci exists and can cause disease commonly. The disease due to this microorganism can be diagnosed by complement fixation or EIA tests using chlamydial group antigen. Specialized laboratories can isolate the organism and also perform microimmunofluorescence tests. A major new development in the evaluation of patients with primary typical pneumonia is the emergence of this Chlamydia psittaci strain that is capable of being passaged from human to human and which may not have the desired response to erythromycin treatment.

ADENOVIRUS PNEUMONIA

Adenoviruses are ubiquitous nonenveloped DNA viruses which colonize the human nasopharynx and are transmitted to other persons by close contact. Types 4 and 7 are recognized for their capacity to produce epidemics in military recruit populations. Since the transmission of this group of viruses is dependent upon close human contact, disease is often produced in the home or the military recruit barracks. Pathogenetically, lung infection usually follows pharyngitis and a movement of the disease process down the respiratory tract. Although most cases of pneumonia are not severe, cases coming to autopsy show that the tracheobronchial mucosa is denuded of the normal epithelial structures down to the basal layer. Squamous metaplasia occurs along with interstitial space thickening due to the presence of chronic inflammatory cells. Alveolar edema and mononuclear cell infiltrates are present. As with Mycoplasma pneumoniae infections, infiltrates are oftentimes peribronchial or peribronchiolar in distribution. Nuclear inclusion bodies or nuclei with a smudged appearance may be found in epithelial cells.

Clinically, the disease oftentimes begins with pharyngitis associated with fever and anterior cervical lymphadenopathy with or without conjunctivitis and then involves the tracheobronchial tree and finally the parenchyma of the lung. Pneumonia is most common in infants, young children and military recruits. In military recruit population, mycoplasma and adenovirus pneumonia have been found to be indistinguishable clinically except for an increased frequency of exudative pharyngitis with adenovirus infection. Physical examination reveals pharyngitis and rhinitis and scattered rales and rhonchi (47). Evidence of consolidation is usually infrequent but occasionally lobar consolidation can occur and also a pleural effusion (48). Virus has been isolated from pleural fluid rarely (2). Fatal cases of adenovirus pneumonia can occur in infants, immunosuppressed patients and rarely in normal persons (49-53). In these cases, the pneumonia is progressive with the development of diffuse bilateral alveolar infiltrates and hypoxemia requiring ventilator assistance for its correction. As the infiltrates progress, leukopenia ensues with marked lymphocytopenia. Rhabdomyolysis occurs along with evidence of disseminated intravascular coagulation and renal failure. Terminally, the patient becomes obtunded.

Bacterial suprainfection can be associated with adenovirus pneumonia. Suprainfecting species of bacteria include Streptococcus pneumoniae, group A streptococci, Hemophilus influenzae, Staphylococcus aureus and group Y Neisseria meningitidis (54). In military recruits, an increased frequency of group Y meningococcal suprainfection has been observed since these microorganisms are common colonizing bacteria of the nasopharynx in this population. Administration of antibiotics during the course of the adenovirus pneumonia does not prevent bacterial suprainfection. Although most persons recover uneventfully from adenovirus pneumonia, occasional patients have residual abnormalities like restrictive lung disease, bronchiectasis, or bronchiolitis obliterans (55-56). Extrapleumonic manifestations of adenovirus infection include pharyngitis, conjunctivitis, pericarditis, arthritis and skin rashes and hepatic dysfunction. Reye's syndrome has been described during the course of adenovirus pneumonia (57). The occurrence of one or more of these manifestations during the course of pneumonia can lead the physician to order appropriate diagnostic tests to make a specific etiologic diagnosis. Virus can be isolated from the nasopharynx, sputum or endotracheal secretions. Antigen can be detected within epithelial cells derived from the respiratory tract by immunofluorescence tests, EIA or DNA hybridization (58). These latter tests are specific but at the present time less sensitive than viral culture. There is no specific therapy for the infection. Oral live attenuated vaccines are available against Types 4 and 7 adenoviruses and these are now used in the military to prevent epidemic disease.

Illustrative Case - Fatal adenovirus pneumonia

The patient was a 32 year old man with an unremarkable past history except for hypertension which was controlled on medication. Two weeks prior to admission he developed a nonproductive, hacking cough and began to have progressive dyspnea. This increased to the time of admission. On physical examination he appeared in moderate respiratory distress. Oral temperature was 38.1°C, pulse rate was 100/min, blood pressure was 170/106, respiratory rate was 30/min. The oropharynx was described as normal. Scattered rhonchi and rales were heard diffusely through the lungs. A summation gallop was heard at the cardiac apex. Laboratory examination revealed a white blood count of 5100 with 82% polymorphonuclear cells, 11% band forms, 3% lymphocytes and 4% monocytes. Arterial blood gases on room air showed a pH of 7.44, pCO_2 of 31 and pO_2 of 56. EKG showed left ventricular hypertrophy. Chest x-ray revealed an enlarged cardiac silhouette with patchy alveolar infiltrates of the entire right lung and left lower lobe.

He was started on erythromycin 500 mg every 6 hours intravenously. He continued to spike temperatures to 40°C. Cefamandole and tobramycin were added to his antibiotic therapy. Two days after admission, the creatine phosphokinase value rose to 16,420 and the next day was 37,576. His creatinine rose to 4.8 mg/dl. His heart was enlarged on x-ray and the pulmonary infiltrates continued to increase. His mental status gradually deteriorated and he was transferred to the Intensive Care Unit. The white blood count was 3700 with 12% lymphocytes. He developed evidence of disseminated intravascular coagulation and died on the eighth hospital day of respiratory insufficiency.

Post-mortem examination revealed changes of viral pneumonia, with some epithelial cells showing intranuclear inclusions and the appearance of "smudged" nuclei, an enlarged heart due to idiopathic myocardial disease, only minimal pathological evidence of hypertension and the presence of findings of disseminated intravascular coagulation. Electron microscopy of lung sections revealed adenovirus. The adenovirus complement fixation test titer rose from < 1:8 to 1:64.

Comment: The patient had a 2-week febrile period before admission and had progression of his pulmonary infiltrates on antibiotic therapy. He developed leukopenia, lymphocytopenia, rhabdomyolysis, disseminated intravascular coagulation and acute renal failure. His illness occurred in the setting of idiopathic myocardial disease and it is possible that mild chronic left sided ventricular failure might have predisposed him to severe adenoviral pneumonia similar to the manner in which cardiac failure augments influenza pneumonia.

PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS, PARAINFLUENZA AND OTHER VIRUSES

Respiratory syncytial virus is the predominant respiratory tract viral pathogen of infancy and young childhood. Infection in adults usually results in no symptoms or a mild upper respiratory tract illness like the common cold. It is now recognized that immunosuppressed patients and elderly persons can develop pneumonia due to RSV and that it can be severe and complicated by bacterial suprainfection (59-61). Furthermore, since immunosuppressed and elderly persons may aggregate in hospitals and nursing homes, these institutions are often sites of acquisition of infection. An epidemic of pneumonia and febrile respiratory illness took place in Los Angeles, California in February-March, 1979 (62). Forty of 101 residents were affected with 22 having pneumonia. Eight persons died for a case-fatality rate of 20%. Other such outbreaks have been recorded. Nosocomial acquisition of RSV is very difficult to prevent. Hospital personnel become colonized and may have no or mild respiratory tract symptoms. Transfer of virus can occur by patient to personnel to patient transmission or directly from the personnel, themselves. Hands and fomites become contaminated by respiratory secretions and virus is spread to patients by direct contact with these sources. The pathology of pneumonia due to RSV is similar to that of other viral pneumonias; however, epithelial cells with intracytoplasmic inclusion bodies can be seen. The x-ray appearance of the pneumonia can be that of a diffuse interstitial process, or have interstitial and patchy alveolar infiltrates in the lower lobes or have an appearance indistinguishable from the adult respiratory distress syndrome.

Pneumonia due to RSV in immunosuppressed and elderly persons represents a newly described phenomenon, but one that may be of increasing importance. It is also important since RSV infections can be diagnosed early by antigen detection techniques (immunofluorescence or EIA) and because effective therapy has recently been developed. Antigen detection tests for RSV now equal or exceed the efficacy of viral cultures for diagnosis of infection. Respiratory syncytial virus infections in infancy have now been treated successfully with aerosolized ribavirin (63-64). This therapy is indicated for infants and children with lower respiratory tract involvement with RSV who are exceptionally ill or who may have congenital heart disease or

bronchopulmonary dysplasia. With aerosol delivery by oxygen tent, hood or mask, concentrations of ribavirin are quite high in the upper and lower respiratory tract and exceed by several-fold the minimum inhibitory concentration necessary to inhibit the growth of the virus in tissue culture. In order to reach this concentration by oral administration of the drug, unacceptable toxicity would be encountered. This toxicity would include bone marrow depression and particularly anemia related both to maturation arrest and to a lesser extent hemolysis. This latter event occurs because ribavirin triphosphate can accumulate in erythrocytes, having a half-life greater than 40 days, and interferes with the formation of guanosine triphosphate. Aerosolized ribavirin therapy is expensive, but is presently approved by the Food and Drug Administration for the therapy of complicated RSV infections in infants and young children. It represents the first example of an effective drug for treating a significant lower respiratory tract viral infection. It is conceivable that this technology could be applied to influenza infections. Influenza and rubeola will be covered in detail but it is now recognized that other RNA viruses can cause lower respiratory tract involvement in adults. These viruses include the parainfluenza viruses, respiratory enteroviruses like Coxsackie B viruses and Coxsackie virus A21, rhinoviruses and coronaviruses (65). The magnitude of the problem, however, appears to be limited. Documented instances of severe lower respiratory tract infection due to parainfluenza II and III viruses have occurred, however. There is no accepted therapy for these latter infections at the present time, although aerosolized ribavirin has been utilized successfully to control persisting parainfluenza virus infections of the lower respiratory tract in immunodeficient children.

INFLUENZA PNEUMONIA

Influenza A virus is the cause of pandemics and epidemics that occur every or every other year. All influenza A viruses possess a common group complement fixation test antigen, the nucleoprotein antigen. Influenza A viruses differ in the antigenic character of the hemagglutinin and neuraminidase. The H0N1 strain of influenza A circulated in the world from 1918-1919 through 1945. H1N1 strains circulated from 1946 through 1957 when Asian influenza strains (H2N2) became predominant. These strains circulated until 1968-1969 when Hong Kong influenza (H3N2) appeared and strains of this virus continue to be transmitted. H1N1 strains again began to circulate during 1976 and they continue to do so. Influenza B strains have the same common complement fixation test antigen and this differs from that of influenza A virus. The hemagglutinin and neuraminidase of influenza B virus are less prone to change; pandemic disease due to this virus does not occur and the interepidemic interval is longer than that of influenza A, namely, every 3-4 years. Serious morbidity due to influenza A virus occurs because of host factors like age, underlying disease and immunosuppression, because immunity wanes with time, and because influenza A viruses are constantly changing their antigenic character. In pandemic years, when both the hemagglutinin and neuraminidase change concomitantly, there is a tendency for more serious disease to occur than if just one of the surface proteins changes. This is well illustrated by the 1918-1919 and 1957 pandemics. Influenza A viruses may, on certain occasions, of themselves be more virulent. In the 1918-1919 epidemic the pneumonia rate in persons aged 25-40 years was approximately 10% of those who had influenza (66). This and other

facts have been cited to indicate the virulence and striking pneumotrophism of the virus which led to 20 million deaths occurring throughout the world during the pandemic. Influenza B viruses are more likely to cause disease in younger persons and only occasionally do epidemics occur in which there is excess mortality.

Pathogenetically, influenza virus attaches to cells of the respiratory epithelium, and enters by a process termed receptor mediated endocytosis. The virion is uncoated in the endosome by fusion with the membrane of this structure, a process requiring an acidic pH. The particle then undergoes a cytoplasmic and a nuclear stage of replication. Virion RNA is capped and polymethylated in the nucleus so that the RNA message now can be recognized by the cell and translated at the ribosome (67). In the process of replication, the virus rapidly destroys respiratory tract epithelial structures so as to compromise natural defense mechanisms of the lung, like mucous production and ciliary activity. In cases of severe pneumonia the epithelium of the trachea and bronchi are destroyed down to the basal layer and then metaplasia occurs, leaving the respiratory tract coated with a layer of squamous cells. There is involvement of bronchiolar structures and an intense peribronchiolar inflammatory process. In uncomplicated influenza, small airways are commonly affected producing diffuse dysfunction in these structures, mild hypoxemia and a compensated respiratory alkalosis (68,69). In severe influenza pneumonia, there is alveolar cell destruction and disruption of the alveolar-capillary membrane resulting in hemorrhage into the alveoli along with edema, a mononuclear cell infiltrate and the presence of hyaline membranes. Thickening of the interstitium occurs with a chronic inflammatory cell infiltrate. The process can be fulminant occurring coincident with the onset of illness, or it can be more protracted leading to the occurrence of progressive infiltrates over 5-7 days. When an adult respiratory distress syndrome-like picture is produced, influenza pneumonia has a high case-fatality rate, which may approximate 75% (70,71). Not all influenza A pneumonia is this severe, however, and there are cases in which only an interstitial or bronchopneumonic process is apparent and the disease simulates mycoplasma pneumonia, except that in influenza the leukocyte count tends to be normal or decreased (72,73). Influenza pneumonia can coexist with bacterial suprainfection or else bacterial suprainfection can occur alone. The offending bacterial pathogens may vary between pandemics; in 1889-1890, Hemophilus influenzae evidently was a major pathogen. In the 1918-1919 pandemic, the group A streptococcus was considered a major pathogen; more recently, Streptococcus pneumoniae has been the most common offending agent followed by Staphylococcus aureus and Hemophilus influenzae. Occasionally, other gram negative bacteria may be involved. Influenza B virus can cause a similar spectrum of pulmonary disease, but the number of patients involved are fewer. The hospitalization rate for lower respiratory tract disease usually always increases during influenza A epidemics. This rate tends not to increase during influenza B epidemics although total hospitalizations may be increased during this period because influenza B virus can cause a variety of disease processes outside the lung similar to influenza A virus. These include myopericarditis, rhabdomyolysis, disseminated intravascular coagulation, nervous system disturbances like encephalitis, Reye's syndrome, the Landry-Guillan-Barre' syndrome, the Stevens-Johnson syndrome and others (4,74).

Clinically, the patient with influenza virus pneumonia has the sudden onset of fever, prostration, and myalgias followed shortly thereafter by dyspnea. Blood-tinged sputum may be produced. The dyspnea progresses until hospitalization and ventilatory support are required. The illness can also assume a more protracted course leading to progressive interstitial and alveolar infiltrates over a week. Some patients simply have viral pneumonia with pulmonary dysfunction but they do not need ventilator assistance. Complicating bacterial suprainfection may coexist with viral pneumonia or more commonly presents after an afebrile interval during which the patient appears to be recovering from the primary infection. Morbidity and mortality are greatest in elderly persons, in those with chronic disease states like chronic obstructive pulmonary disease, or chronic congestive heart failure or diabetes mellitus and in immunosuppressed patients. Morbidity due to influenza A and B viruses are not limited to these groups, however. Women in the third trimester of pregnancy may also have an increased rate of developing influenza pneumonia and death due to that disease process (75). In renal transplant recipients who contract influenza A, illnesses are ofentimes prolonged, with the development of viral pneumonia, bacterial suprainfection and myopericarditis. There may be loss of the renal allograft due to the combination of these disease processes (76). Influenza A and B virus infections are diagnosed by serial titer rises in a suitable serological test like the complement fixation or the hemagglutination inhibition test. A single complement fixation test titer $\geq$ 1:128 has been shown to correlate highly with recent influenza B infections (4). Virus can be grown from the nasopharynx or endotracheal secretions by inoculation of the specimen into Rhesus monkey kidney or Madin-Darby canine kidney tissue culture. Embryonated eggs sometimes need to be used for optimal recovery of virus. Virus may be able to be identified within 72 hours by using immunofluorescence. Direct detection of antigen by immunofluorescence or EIA can be applied to appropriate secretions but these tests are not yet as sensitive as viral culture (77).

Amantadine and rimantadine are two compounds that have both prophylactic and therapeutic efficacy against influenza A but not influenza B virus. They act by preventing uncoating of influenza A virus perhaps by preventing the development of an acidic pH so that the envelope of the virion cannot fuse with the endosomal membrane. At the disage given, 100 mg twice as day, amantadine has more central nervous system side effects and the dose has to be adjusted with renal failure (78). The dose of rimantadine does not have to be adjusted with renal dysfunction because the compound is metabolized in the body. A study sponsored by the National Institutes of Health is underway evaluating whether rimantadine can be used effectively in the therapy of hospitalized patients with influenza A and would include patients with influenza A virus pneumonia. Ribavirin has *in vitro* efficacy against both influenza A and B viruses. It has multiple sites of action including interference with the formation of guanosine triphosphate and deoxyguanosine triphosphate and prevents placement of the polymethylated cap structure on the influenza A viral RNA message. With the aerosolization of ribavirin, high concentrations of the drug can be produced within the respiratory tract but serum levels are low (79,80). Attempts, most likely, will be made in the future to treat influenza A virus pneumonia with aerosolized ribavirin or a combination of ribavirin and rimantidine. Influenza B virus pneumonia may be able to be treated with aerosolized ribavirin. Vaccines exist for both influenza A and B viruses and standard medical care necessitates yearly

immunization of elderly patients or those with underlying medical conditions. A recent emphasis of the Public Health Service is to have medical personnel also immunized yearly since they are exposed to persons with influenza, may develop that illness, themselves, and then transmit the infection to sick patients within the hospital.

Illustrative Case - Nosocomial influenza pneumonia

This 55 year old alcoholic man was admitted into the hospital on January 30 with alcoholic liver disease, macrocytic anemia and symptoms of vesicle neck obstruction. He was a heavy smoker and had evidence of chronic obstructive pulmonary disease. Twelve days after admission into the hospital while awaiting a urological procedure he developed fever to 39.2°C. He "felt terrible" with myalgias and developed a cough, mild diarrhea and dyspnea. Chest exam revealed diffuse rales and rhonchi. Chest x-ray showed new interstitial infiltrates, more prominent on the right. The sputum was mucoid. The diagnosis of pneumonia was made and the diagnosis of congestive heart failure with pulmonary edema considered. However, his heart exam revealed no gallop sounds and his neck veins were not distended. He was placed on ampicillin, became afebrile after 5 days and his dyspnea improved with low flow oxygen by face mask. Influenza A complement fixation test titer on a single convalescent serum specim was $\geq$ 1:256.

Comment: Influenza virus pneumonia incurred during hospitalization. The pneumonia cleared with symptomatic therapy. The Public Health Service now recommends widespread immunization of medical personnel in an attempt to prevent nosocomial acquisition of influenza.

MEASLES PNEUMONIA

Although predictions were made that rubeola would be eradicated in this country during the early 1980 period, this has not been achieved and in Dallas, Texas during 1986 over 150 cases of rubeola occurred. This marked a resurgence of cases after a relatively disease free interval after 1971 when a large epidemic occurred in Dallas, which caused more than 1000 cases, including 3 deaths. As a consequence of this and other epidemics, Texas adopted a law requiring the compulsory immunization of children against measles, mumps, rubella, poliomyelitis, diphtheria and tetanus in 1971. Present rubeola vaccines are, at least, 95% effective, but universal immunization of the preschool child is not practiced, particularly in lower socioeconomic class population groups. Furthermore, rubeola virus, has been found to violate the concept of herd immunity, a major principle on which eradication was based, since outbreaks occur in high schools and colleges in which a large percentage of the population has been immunized. An inactivated vaccine was available from 1962 through 1965. Children receiving the inactivated vaccine may develop atypical measles on exposure to rubeola virus. Following this, an attenuated, live strain of measles virus was used as vaccine but the high side-reaction frequency necessitated the concomitant administration of γ-globulin. It is now recognized that the concurrent use of γ-globulin sometimes rendered immunization ineffective. Many children were immunized before the age of 12 months and it is now apparent that in order for effective immunization to occur, vaccine must be given after the age of 15 months. As a consequence of the lack of universal preschool

immunization and difficulties related with the vaccine, there now exist two population groups who may be non-immune with respect to rubeola, viz., preschool children and adolescents and young adults. A few years ago rubeola epidemics were common in military recruits. Following the occurrence of these outbreaks, recruits now routinely undergo serological testing, and if antibody to rubeola virus is not detected by either hemagglutination inhibition or indirect immunofluorescence tests live, attenuated vaccine is given. This practice has essentially stopped the occurrence of these outbreaks in the military.

Persons who received the inactivated vaccine can develop atypical measles. The first cases of this new syndrome were misdiagnosed as Rocky Mountain Spotted Fever. They were confused with this disease because the rash began on the extremities and spread inward to involve the trunk. The rash could be maculopapular, vesicular or petechial. In atypical measles, pulmonary involvement consists of nodular infiltrates, lobar consolidation and the occurrence of pleural effusions. Hilar lymphadenopathy may also present in these patients (81,82). They have an anamnestic response in antibody production with the infection. Mild eosinophilia may also be present and the virus cannot be recovered from the nasopharynx. In young adults with typical measles, approximately 5% develop clinical evidence of pneumonia. Radiographic evidence of pneumonia, however, may be seen in up to 50% of the patients. The pneumonia is usually characterized by diffuse bilateral interstitial or fine reticulonodular infiltrates, particularly affecting the lower lobes. Bacterial suprainfection occurs in as many as 30% of cases of recognized viral pneumonia. The types of bacteria causing infection may be determined by the circumstances in which disease occurs like military recruit populations. Recognized pathogens include Haemophilus influenzae, Streptococcus pneumoniae, group A streptococci, group Y meningococci, and Staphylococcus aureus. Bacterial suprainfection generally occurs between the fifth and tenth days after the rash and is heralded by clinical worsening, new or different lung infiltrates, or changes in sputum characteristics or the white blood count. Antibiotic treatment of viral pneumonia does not prevent bacterial suprainfection.

In immunodeficient children, measles pneumonia occurred without a rash and pathologically was called giant cell pneumonia. It is now recognized that these children lacked cell mediated immunity and had depressed and delayed antibody production (83). Intact cell mediated immunity is essential for rash production. In fatal rubeola pneumonia, the entire tracheobronchial tree may be denuded of cells down to the basal layer, squamous metaplasia of the cells occurs, there is widening of the interstitial space with edema and inflammatory cells and alveoli are filled with edema, hyaline membranes and mononuclear cells. In addition, giant cells containing multiple nuclei are found within the tracheobronchial epithelium. Extrapulmonic manifestations of measles occur and include otitis media, sinusitis, encephalitis, and the common presence of hepatic dysfunction in young adults, mostly consisting of mild elevations of the serum aspartate aminotransferase and lactic dehydrogenase. There is no specific therapy at the present time. Some public health authorities now think that reimmunization with measles, mumps and rubella vaccines should be given before or when the child enters high school. Medical personnel not sure of their rubeola immunity should have that status assessed by determination of specific antibody.

PNEUMONIA DUE TO VARICELLA-ZOSTER VIRUS

Varicella-Zoster virus can produce pneumonia during the course of varicella or disseminated herpes zoster and can be a severe disease which can lead to mortality. Varicella in childhood is not usually associated with viral pneumonia but bacterial suprainfection can occur, necessitating appropriate antibiotic treatment. In immunosuppressed children, however, pure viral pneumonia can occur in association with varicella. In adults, there is a tendency for the virus to affect the lung relatively commonly during varicella. Fifteen-20% of all adults with varicella may have x-ray evidence of pneumonia but only about 5% require hospitalization. Most frequently in adults, varicella pneumonia is not complicated by bacterial suprainfection, however, this can occur particulary when patients require intubation. The virus reaches the lung both by passage down the respiratory tract and by hematogenous seeding since the rash is occurring at the same time as the pneumonia. Initially, the pneumonic process appears as nodular infiltrates, 1-4 mm in diameter associated with an interstitial inflammatory infiltrate (84). The lesions are more dense toward the hilum and are the counterpart in the lung of the pox occurring on the skin. Peribronchial inflammatory infiltrates, hilar adenopathy and pleural effusions may occur. The reticulonodular interstitial infiltrate can progress to widespread alveolar damage and diffuse pulmonary parenchymal infiltrates. Pathologically, the initial nodular infiltrate in the lung consists of an area of coagulative necrosis in which cells with enlarged and distorted nuclei and Cowdry type A inclusion bodies can be seen. Although these necrotic areas generally clear during the course of clinical disease, they can become calcified and the x-ray then shows a picture of miliary calcifications. It has been shown that this area of coagulative necrosis can become surrounded by an inflammatory infiltrate and resemble a granuloma (85). Fibrous tissue envelopes the necrotic granulomatous process and the lesion eventually calcifies. Another process occurring in varicella pneumonia is destruction of the epithelium of the trachea and bronchi. In cases in which the illness is protracted, the development of a thick, fibrinopurulent crust may occur over the lower pharynx, larynx and upper trachea. This thick crust can cause respiratory embarrassment and can pose a problem for intubation. Disseminated herpes zoster can cause the same processes in the lung. Most normal adults recover from varicella pneumonia without difficulty, but there can be substantial respiratory morbidity and mortality in immunosuppressed patients or in women during the third trimester of pregnancy (86).

Clinically, the patient with varicella-zoster virus pneumonia presents with a rash followed soon thereafter by cough and dyspnea. The sputum is initially white in color and modest in amount but can become hemorrhagic. The process can be complicated by the development of chest pain and pleural effusions which are often blood-tinged and which are related to the presence of pox on the pleural surface. Extrapulmonic manifestations of varicella occur and consist of the characteristic skin rash, otitis media with bacterial suprainfection, myopericarditis, hepatic dysfunction, and encephalitis. Reye's syndrome can complicate the course of varicella. There can be an associated glomerulonephritis and varicella virus can occasionally induce frank arthritis. In caring for patients with varicella-zoster virus pneumonia, it is important to realize that the external appearance of the patient or his apparent well-being may disguise underlying hypoxemia. If

efforts are not made to diagnose and correct the hypoxemia, the patient may become confused, perform inappropriate activity, and become more hypoxemic. Ventilator support may become necessary. Deaths in varicella pneumonia occur because of respiratory insufficiency, the development of tension pneumothoraces, bacterial suprainfection or because of progressive pulmonary fibrosis.

Two antiviral compounds, adenine arabinoside (Ara-A) and acyclovir (ACV), have been proven to be of efficacy in the treatment of significant, complicated varicella-zoster virus infections. Adenine arabinoside inhibits viral DNA polymerase and is given at a dosage of 10 mg/kg over a 12 hour period for a least five days. The dose could be increased to 15 mg/kg but the majority of experience with varicella-zoster virus infections is with 10 mg/kg/day. The drug is sparingly soluble so that 2 ml of vehicle are required for each mg of drug administered to the patient. At a dose of 10 mg/kg, bone marrow suppression does not usually occur. If the dose is not decreased in the setting of hepatic and renal dysfunction, central nervous system disturbances may occur and which consist of insomnia, hallucinations and tremulousness. These central nervous system manifestations usually fade with stopping the drug but can persist for a protracted period after the drug has been discontinued and rarely lead to death. Acyclovir has also been used to treat varicella-zoster virus infections. It inhibits viral DNA polymerase and also acts as a chain terminator. Its does is 500 mg/M^2 every 8 hours for at least 7 days. The only significant problem with the administration with acyclovir in this setting is the production of an obstructive nephropathy, due to salting out of the drug in the collecting tubules of the kidney. This is usually easily managed by administration of a fluid bolus, or a diuretic or the administration of mannitol. A comparison of the two drugs in complicated varicella-zoster virus infection has been made (87,88). One group found that acyclovir was more efficacious but the other study determined that Ara-A was equally as effective. Since the administration of Ara-A requires an increased volume of fluid and can be associated with central nervous system side effects, some authorities now consider acyclovir the drug of choice in the treatment of complicated infections due to varicella-zoster virus. Oral acyclovir is poorly absorbed by the gastrointestinal tract and its efficacy in uncomplicated herpes zoster is apparent only when 800 mg are given 5 times a day for at least a 5 day period. There has been no experience with oral ACV in treating varicella pneumonia. Future modes of therapy may include combining Ara-A with ACV or administering one or other of the drugs with an interferon preparation. Alpha-interferon has also been shown to be effective as therapy in complicated varicella-zoster virus infections but its use has been superceded by ACV and Ara-A.

Illustrative Case - Varicella pneumonia

The patient was a 39 year-old man who was exposed to his 2 children with chicken pox. Two days prior to admission he developed a rash and soon thereafter dyspnea. On physical examination, a typical varicella rash was present. He was in severe respiratory distress. Rales were present diffusely over both lung fields. The chest x-ray revealed bilateral extensive alveolar infiltrates. Arterial blood gases showed a pH of 7.42, pCO_2 of 32 and a pO_2 of 24. He was intubated, begun on positive end-expiratory pressure (PEEP) with a FIO_2 of 70%. He was started on

intravenous acyclovir 500 mg/M^2 every 8 hours. He improved and was able to be extubated after 5 days.

Comment: Severe varicella pneumonia responding to intravenous acyclovir while his oxygenation was maintained on PEEP with a high FIO_2.

PNEUMONIA DUE TO HERPES SIMPLEX VIRUS AND EPSTEIN-BARR VIRUS

Herpes simplex virus can cause a necrotizing bronchopenumonia in neonatal infections and can also cause pneumonia in severely immunosuppressed adult patients. The largest series of patients with herpes simplex virus pneumonia was reported from Seattle in bone marrow transplant recipients and consisted of 20 patients with either a focal pneumonia (12 patients) or a diffuse intersititial pneumonia (8 patients) (89). The focal pneumonia was found associated with herpetic esophagitis and tracheitis and probably resulted from contiguous spread of herpesvirus to the lung parenchyma. Diffuse interstitial pneumonia most probably resulted from hematogenous dissemination of virus to lung. Pathologically, the process can be one of a necrotizing bronchopneumonia or as a widening of the interstitial space in the lung associated with diffuse alveolar injury. In these highly immunosuppressed patients, both bacterial and fungal suprainfection occurred and it was difficult to sort out which of the processes was responsible for what proportion of lung damage. Acyclovir has been shown to be an effective treatment of complicated herpes simplex virus infections in immunosuppressed patients. Its dose in the usual patient is 250 mg/M^2 every 8 hours for at least a 7 day period of time but if the process has been ascertained to be a rapidly progressive herpetic pneumonia, the dose could be increased up to 10 mg/kg every 8 hours until a therapeutic response had been obtained. With the development of potent antiviral chemotherapy, there is a need to consider and diagnose herpetic pneumonia. Specific diagnosis can only be accomplished readily by lung biopsy.

Although involvement of the lung in infectious mononucleosis due to Epstein-Barr virus must be considered a rare occurrence, recent studies and case reports demonstrate that it probably can happen (90,91). Careful attention should be given to possible coexisting mycoplasma and other viral infections, particularly since the former can be treated. Radiographic abnormalities may consist of hilar adenopathy, strand-like parenchymal infiltrates, diffuse bilateral pneumonia and a picture consistent with primary atypical pneumonia. Although Epstein-Barr virus is susceptible to acyclovir, there are no reports treating lung involvement with this drug.

CYTOMEGALOVIRUS PNEUMONIA

Cytomegalovirus (CMV) rarely causes pneumonia in normal adults as part of the CMV mononucleosis syndrome (92). However, it is more common for CMV to induce pneumonia in normal hosts than Epstein-Barr virus. Of 443 patients with community acquired pneumonia, 18 had virological (2), pathological (2) or serological (14) evidence of CMV infection (93). Ten of these 18 patients were not immunosuppressed. In 5 of the 10, CMV was the only pathogen. The remaining 5 patients had one or more coexisting infections; C. trachomatis

in 2, M. pneumoniae in 1, Epstein-Barr virus in 1 and bacteria in 3, both aerobic and anaerobic.

Cytomegalovirus more commonly causes pneumonia in immunosuppressed patients. It occurs particularly in renal, heart, liver, and bone marrow transplant recipients. It is now becoming an increasing problem with patients with AIDS. In the transplant recipient experiencing a primary CMV infection, the virus, most probably, reaches the lung parenchyma via the hematogenous route and the first finding is that of a reticulonodular infiltrate and the presence of 1-4 mm opacities. Pathologically, these focal areas usually consist of necrotic tissue, hemorrhage and alveolar damage with edema, a mononuclear infiltrate and typical cytomegalic cells. The process can extend leading to diffuse interstitial and alveolar infiltrates. An attempt has been made to separate the foregoing process from that of an insidiously developing interstitial pneumonia which occurs more commonly in reactivated infections and which has a better prognosis (94). In bone marrow transplant recipients, diffuse interstitial pneumonitis due to CMV is much more common in patients receiving allogeneic marrow transplants and the case-fatality rate approximates 90% (95). In some renal transplant recipients, the pneumonic process can be focal and does not have to be exceptionally severe (96). Small pleural effusions can occur occasionally. In other renal transplants, however, CMV pneumonia can be rapidly progressive and lead to death as part of a widely disseminated infectious process (97). In cardiac transplant recipients a variety of pulmonary opportunistic suprainfections have been well documented to occur in the course of CMV pneumonia (98). Typical microorganisms causing suprainfections include Pneumocystis carinii and nocardia species. In patients with AIDS, there may be co-existing infection with pneumocystis. Cure of the pneumocystis can be effected by drugs leaving CMV as the major pulmonary pathogen. In patients with AIDS, rapid development of CMV pneumonia can occur and lead to the death of the patient. Extrapulmonic manifestations of CMV in the renal transplant recipient include fever, malaise, hepatic dysfunction, splenomegaly, leukopenia, and an increase in serum creatinine (96). With extensive CMV dissemination in heavily immunosuppressed patients, including those with AIDS, extrapulmonic manifestations include gastrointestinal ulceration with bleeding and perforation, hepatic dysfunction, adrenal cortical involvement and central nervous system dysfunction. Cytomegalovirus can be conceived of as an immunosuppressive viral agent and infection with this microorganism may lead to further immunosuppression with consequent bacterial, fungal and parasitic suprainfection.

Clinically, patients with CMV pneumonia complain of dyspnea with a non-productive cough. There can be an associated pleurisy. The process can be transient or can extend to respiratory insufficiency necessitating ventilatory support. Therapy of fully developed CMV pneumonia has been shown not to be effective and this includes the use of the adenine arabinoside, acyclovir, ganciclovir (DHPG), and combinations of interferon with all the above. Ganciclovir has been successful in achieving an antiviral effect in the lung, yet has not improved outcome in bone marrow transplant recipients with CMV pneumonia (99). In an occasional renal transplant recipient who has a the potential of a good immune response to the virus, the CMV illness which can include localized pneumonia might be benefited by the judicious use of ganciclovir. Attempts at prevention of CMV pneumonia have included donor selection, avoidance of white blood cell transfusions, prophylactic

administration of alpha-interferon, or γ-globulin preparations, given before and through the first 60 days after transplantation. Alpha-interferon does prevent CMV viremia in the renal transplant recipient; γ-globulin protects partially against CMV pneumonia if white blood cell transfusions have not been given. Studies are in progress trying to make this latter effect more consistent and consist of determining whether total antibody content is the necessary component or whether the effect necessitates the presence of large quantities of neutralizing antibody. On a priority basis, live, attenuated CMV vaccine development has been curtailed for the immediate future.

Illustrative Case - Fatal CMV pneumonia

This 40 year old homosexual man presented to the hospital with fever, cough and an erythematous rash. He had been followed in clinic as a case of AIDS related complex (ARC) with lymphadenopathy, thrush, lymphopenia, anergy, diarrhea, and a positive antibody test to human immunodeficiency virus. At the time of his acute terminal illness he had a temperature of 38.5°C and had a diffuse, erythematous pruritic rash over the trunk and upper legs. The admission chest x-ray was interpreted as normal. On the second hospital day, the patient became delirious, had a worsening cough and developed severe dyspnea. Arterial blood gases on room air revealed a pH of 7.50, pCO_2 of 30 and a pO_2 of 44. Chest x-ray now revealed bilateral diffuse reticulonodular infiltrates. He was started on sulfatrimethoprim but had a respiratory arrest and expired. Post-mortem exam revealed CMV pneumonia without evidence of pneumocystis. Lung viral cultures rapidly grew CMV, with the cytopathic effect being present the second day.

Comment: Explosive illness in a patient with ARC revealed only CMV at autopsy and on viral culture of the lung.

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