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# *Acute Respiratory Infections*

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“I am at this moment,  
Deaf in the ears,  
Hoarse in the throat,  
Red in the nose,  
Green in the gills,  
Damp in the eyes,  
Twitchy in the joints,  
And fractious in temper  
From a most intolerable  
And oppressive cold.”

NO ONE BEFORE OR SINCE Charles Dickens has improved on this description he gave of acute respiratory infection, which constitutes by far the most common illness of man encountered in the world. Adults lose more time from work due to these infections than to any other single condition; children lose time from school. Although the incidence of illness is extremely high, the death rate due to acute respiratory disease is low.

Acute respiratory infections comprise a spectrum of diseases ranging from a mild case of the common cold to serious bronchopneumonia or empyema. Any respiratory pathogen or group of pathogens can be associated with a variety of clinical syndromes, and any clinical syndrome may be produced by a number of respiratory pathogens. Although most acute respiratory infections are due to known viruses, many viral agents remain unknown, and clinical observation alone cannot determine the etiologic agent in a given patient. Even under optimal circumstances it is difficult to confirm the presence of viral agents during the acute phase of illness, when such information would be most helpful. In the Cleveland family study, Dingle found that respiratory infections accounted for two thirds of the total illness in the community; approximately 97% of these infections were due to a virus.

The complexity of the problem becomes compounded when one realizes that the small percentage of cases which are not due to viruses might be associated with bacteria, fungi, protozoa, rickettsia or mycoplasma. The culturing of bacteria, fungi or mycoplasma from the pharynx or nasopharynx does not necessarily establish those organisms as the cause of disease. Since some of these organisms are susceptible to antimicrobials, the clinician must be astute in determining which infections need therapy.

The type of illness produced by a respiratory pathogen varies with the host and the environment. Age is significant; certain young children will respond to a variety of viral agents with a characteristic clinical syndrome, whereas older children may respond with a different clinical disease when exposed to the same viruses. Individual variation of response occurs; some persons will acquire an upper respiratory infection when exposed to respiratory pathogens, whereas other persons might have a more severe lower respiratory infection when exposed to the same pathogens. Some persons will have up to ten

TABLE I.—NORMAL MICROBIAL POPULATION OF THE UPPER RESPIRATORY TRACT\*

	NASAL PASSAGES†	NASO- PHARYNX‡	OROPHARYNX- TONSIL‡
Gram-positive cocci			
Coagulase-negative staphylococci	++	++	±
Coagulase-positive staphylococci	++	++	++
Anaerobic micrococci and streptococci			+
<i>Streptococcus mitis</i> and other $\alpha$ - and $\gamma$ -streptococci	±	++	++
<i>Streptococcus hominis</i> (salivarius)		+	++
<i>Streptococcus pyogenes</i>	±	±	++
<i>Diplococcus pneumoniae</i>	+	+	++
Gram-negative cocci			
<i>Neisseria catarrhalis</i> and other spp.	+	++	++
<i>Neisseria meningitidis</i>		+	
<i>Vibrio alcalescens</i>		+	+
Gram-positive bacilli			
Aerobic corynebacteria	++	+	+
<i>Corynebacterium acnes</i>	+		
Mycobacteria	±	±	±
<i>Actinomyces israeli</i>			+
Aerobic gram-negative bacilli			
Undifferentiated "coliforms"		++	+
<i>Escherichia coli</i>		±	
<i>Klebsiella aerogenes</i>		±	+
<i>Proteus mirabilis</i> , other spp.			+
<i>Pseudomonas aeruginosa</i>			±
<i>Moraxella lacunata</i>	+	±	
<i>Mima polymorpha</i> and <i>Mima vaginicola</i>		±	
<i>Haemophilus influenzae</i>	+	++	++
<i>Haemophilus parainfluenzae</i>		+	++
Hemolytic hemophili		+	++

Anaerobic gram-negative bacilli, vibrios, spirilla and spirochetes		
<i>Bacteroides fragilis</i> , other species	+	+
<i>Fusobacterium fusiforme</i>		+
<i>Spirillum sputigenum</i>	+	
<i>Vibrio sputorum</i>	+	±
<i>Treponema dentium</i> and <i>Borrelia refringens</i>	+	
Fungi		
<i>Candida albicans</i>		+
Other candidas		+
<i>Torulopsis glabrata</i>		±
Protozoa		
<i>Entamoeba gingivalis</i>		+
<i>Trichomonas tenax</i>		+
Mycoplasmas		
<i>Mycoplasma hominis</i>	±	+
<i>Mycoplasma orale</i> 1 and 2	+	++
<i>Mycoplasma salivarium</i>	+	++
<i>Mycoplasma pneumoniae</i>	±	±
T-strains	+	+
Viruses		
Adenoviruses	+	±
<i>Herpesvirus hominis</i>	+	±

\*From Cherry, J. D.: Newer Respiratory Viruses, in Schulman, I.: *Advances in Pediatrics* (Chicago: Year Book Medical Publishers, Inc., 1973), Vol. 20.

†±, irregular; +, common; ++, prominent

infections a year and others will have only one or two. Other factors affecting the frequency and type of illness a person might acquire include allergy, the presence of cardiopulmonary disease, genetic predisposition, geographic location, prior exposure to the same agent, physiologic state of the person, personal habits and season of the year.

The communicability of the respiratory pathogen depends on the agent itself and the setting in which it is found. Certain agents spread poorly (adenoviruses, Epstein-Barr virus, *Mycoplasma pneumoniae*); however, with close and prolonged contact or with crowding and poor personal hygiene, spread of these agents to susceptible contacts occurs. On the other hand, in open communities with considerable mobility of inhabitants, the transmission of respiratory agents may be limited.

Since the introduction of the germ theory approximately 100 years ago, it has been pointed out that many kinds of microbes are always present in the bodies of healthy men and animals. It is appropriate to emphasize that "infection" and "illness" are not synonymous, since asymptomatic infections occur frequently with many bacteria, mycoplasma and viruses. The so-called normal flora (Table 1) is continually changing and new strains of organisms replace their predecessors. Frequently, the flora is composed of potentially pathogenic organisms. The interplay (synergism and anergism) of the total microbial popu-

lation of the body is most likely an important factor in the determination of whether or not new infectious agents might enter the body and of the state of well-being or disease.

Although many infectious agents have been etiologically associated with specific diseases (*Streptococcus pneumococcus* with pneumonitis, Group A  $\beta$ -hemolytic streptococcus with scarlet fever, respiratory syncytial virus with bronchiolitis), the actual pathogenesis of these illnesses is not well established. The most convincing evidence associating specific viruses with specific diseases occurs with the recovery of a specific virus from a statistically greater number of persons with disease than from a control group without disease when there is an outbreak of disease such as croup, pneumonia or bronchiolitis in a community.

Although many of the viruses causing acute respiratory disease have been identified, effective vaccines for prevention of disease are still, for the most part, not available. The most progress made in the production of an effective vaccine has been with influenza agents; however, influenza vaccines may be successful one season and not sufficiently antigenic to produce protection in subsequent seasons.

## ETIOLOGY OF RESPIRATORY TRACT INFECTIONS

### VIRUSES

Our knowledge about the etiology of acute respiratory disease is incomplete since over half of the cases, even in carefully studied epidemics, fail to yield an identifiable agent. Most of the viruses believed to cause respiratory disease have an extremely short survival when removed from the living cell and they may not survive to be identified. Known viruses responsible for respiratory infections are listed in Table 2. Although viruses causing smallpox, measles and mumps may cause symptoms of acute respiratory disease, their major manifestations are due to involvement of other systems and they are excluded from the group of respiratory agents. Information from surveys of respiratory infections will depend on the technics available when the infections or epidemics are occurring.

**MYXOVIRUSES.**—The myxoviruses implicated in acute respiratory disease include influenza viruses, parainfluenza viruses and respiratory syncytial virus. These viruses are of medium size, ranging from 80 to 300 nanometers (nm), possess essential lipids and a RNA core arranged in a helix, are either sensitive and acid labile and have the capacity to produce hemagglutination, hemadsorption and virus elution. The cytopathic effect caused by these viruses consists of the formation of syncytia or giant cells or the viruses may lyse the cell.

**Influenza viruses.**—The influenza viruses were the first of the respiratory viruses to be discovered: influenza A by Smith, Andrews and Laidlaw in 1933, influenza B by Francis and by Magill in 1940

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TABLE 2.—VIRUSES ASSOCIATED WITH  
ACUTE RESPIRATORY DISEASE

Adenovirus  
Coronavirus  
Herpesviruses  
  Herpes simplex  
  Herpes varicella-zoster  
  Herpes cytomegalovirus  
  Epstein-Barr virus  
Lymphocytic choriomeningitis virus  
Myxovirus  
  Influenza virus  
  Parainfluenza virus  
  Respiratory syncytial virus  
Picornavirus  
  Enteroviruses  
  Coxsackie viruses groups A and B  
  Rhinovirus  
Reovirus

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and influenza C by Taylor in 1949. The influenza viruses form separate and distinct antigenic types, and types A and B are composed of individual strains that differ in their immunologic properties. Antigenic variation is a common characteristic of influenza viruses A and B.

Epidemics and pandemics are associated with group A infections, and sporadic and limited outbreaks occur with group B infections. Classically, epidemics of influenza type A occur every 2–3 years whereas influenza type B epidemics occur every 4–5 years. It would appear that epidemics occur when the existing “herd” immunity reaches a point low enough to allow the number of cases to increase to epidemic proportions. In each of the past 4 decades major variants of influenza A have appeared whose dominant antigen was relatively new to most populations.

Influenza type B has two families, but the antigenic variation between them is minor. Little is known about influenza type C, and outbreaks of disease with this agent are usually limited to young children and to persons in military installations.

*Parainfluenza viruses.*—The four known parainfluenza viruses were discovered between 1956 and 1958; significant disease is limited to the first three types. They have worldwide distribution and affect both children and adults. Original infection with these agents occurs early in life so that by age 11 most children have antibody to the four virus types. Although epidemics of illness in closed populations have been due to parainfluenza viruses, the characteristic occurrence is endemic or sporadic. Reinfection can and does occur, resulting in either mild upper respiratory tract disease or asymptomatic infection. Community outbreaks occur in preschool children but are recognized as mild dis-

ease unless the infection is manifested as croup, bronchiolitis or pneumonia. In the adult the disease usually presents as a mild "common cold" or nonexudative pharyngitis.

*Respiratory syncytial virus.*—Respiratory syncytial virus, originally recovered in 1956 from a chimpanzee with coryza and called "the chimpanzee coryza agent," is the major single cause of viral respiratory tract illness during early life. In the United States more than half of the children over the age of 4 years and almost 100% of adults show evidence of previous infection with this agent.

Although primary infection usually occurs in infancy, reinfection causing mild, coldlike symptoms may occur throughout adult life and the level of antibody appears to be inversely proportional to the severity of disease. Subclinical infections occur in both children and adults, usually in the cold weather months. Newborns have transplacentally acquired serum antibody to respiratory syncytial virus, but infection and illness in the presence of this antibody is common. Although antigenic differences between RSV viral strains have been demonstrated, no difference in human antibody resulting from the different antigenic strains has been shown.

The clinical syndromes commonly associated with RSV include upper respiratory infection, croup, bronchitis, bronchiolitis and pneumonia.

**ADENOVIRUSES.**—The adenoviruses are so named because of their preference for multiplication in glandular tissue. There are at least 77 antigenic types isolated from human beings, monkeys, other mammals and chickens. This group of viruses shares a common complement-fixing antigen, permitting serologic diagnosis with a single complement fixation test. They are 70–80 nm. in diameter, contain DNA, are resistant to ether and have cubic symmetry.

Human adenoviruses causing respiratory disease can be divided into two groups. The first group includes primarily types 1, 2, 5 and 6, which are most often found in tonsils and adenoids of apparently healthy persons. Specific antibodies most likely protect the host from frequent attacks of disease with these agents but do not prevent the virus from surviving. These viruses produce upper and probably lower respiratory tract disease in infants and children.

The second group includes primarily types 3, 4, 7, 14 and 21. These agents most frequently cause acute respiratory disease in military recruits, and sometimes certain of these agents cause lower respiratory disease in infants and other civilians. Types 7 and 8 have been associated with pharyngo-conjunctival fever in children, and types 3, 6, 7 and 10, among others, have been associated with an acute follicular conjunctivitis. Illnesses due to adenoviruses occur in all seasons of the year, with peaks of disease in December and January and in June and July.

No more than 10% of the cases of respiratory illness in civilian

populations is due to adenoviruses, whereas among military recruits, the incidence may range as high as 50% of cases, especially when epidemics occur.

**PICORNAVIRUSES.**—The “picornaviruses” (“pico” means very small, “rna” identifies the RNA core) measure between 15 and 30 nm. in diameter, lack essential lipids, are resistant to ether and resist thermal inactivation; they have a rounded or cuboid shape. Agents so far isolated from the nose, throat and stool replicate best in human or monkey cells.

**Rhinoviruses.**—At present there are more than 89 distinct serotypes of rhinoviruses. These agents are ubiquitous and demonstrate a distinctive seasonal pattern, with infection being common in the fall, late winter and spring. Epidemiologic investigations indicate that rhinoviruses can cause common colds and upper respiratory tract infections in adults and children and, occasionally, lower respiratory tract infections in children. Studies with volunteers have shown that antibody is protective, but is type specific with little cross-protection. Immunity probably lasts no more than a year.

**Enteroviruses.**—The enteroviruses include groups A and B Coxsackie viruses, ECHO viruses and polioviruses. Although the major clinical role of enteroviruses is in causing diverse central nervous system syndromes such as aseptic meningitis, meningoencephalitis and paralysis, certain enteroviruses have been associated with acute respiratory infections. Group A Coxsackie viruses have been associated with herpangina (types 2, 4, 5, 6, 8 and 10), a specific clinical syndrome. Coxsackie virus group A, type 21 (Coe virus), is a cause of mild upper respiratory infections in military recruits and young civilian adults. Epidemics have occurred during early fall and during late fall and winter. Coxsackie virus group A, type 16, has been associated with hand, foot and mouth disease (enanthema and exanthema) in Toronto, Ontario; Birmingham, England; and southern California.

Coxsackie viruses group B produce epidemic pleurodynia, whose symptomatology may mimic either acute abdomen or pneumonia. These agents have also been associated with primary pneumonia, bronchiolitis and bronchitis in infants under age 2 years.

ECHO viruses types 1, 3, 6, 11 and 20 have been associated with mild upper respiratory infections and ECHO virus type 11 has on occasion been associated with croup in children and sore throat and fever in adults.

**CORONAVIRUSES.**—The newest group of agents known to cause the “common cold” in man are the coronaviruses. The coronaviruses are sensitive to ether, have an RNA core and measure 80–160 nm. in diameter; they were first isolated from human beings in 1960. Because of the difficulties associated with studying these agents in the laboratory (human embryo tracheal organ cultures are used),



both the incidence of association between these viruses and human illness and the spectrum of disease they may cause are not yet known.

**REOVIRUSES.**—Reoviruses (respiratory enteric orphan virus) were first thought to be ECHO virus type 10 because of similarities between the two (RNA core, cubic symmetry and ether resistance); however, the reoviruses are larger agents (55–75 nm.) than the enteroviruses. Three serotypes exist. Mild or asymptomatic infection with reoviruses in human beings, primarily children, and in many animals is common. The role of reoviruses in regard to respiratory illness is unclear, but they probably do not constitute an important cause of clinical illness.

**HERPESVIRUSES.**—Herpesviruses possess a DNA core, are sensitive to ether and to acid pH and in infected cells form Cowdry type A intranuclear inclusion bodies surrounded by margined chromatin. The virus is 100 nm. in diameter with an icosahedral structure, may be enclosed in an envelope (180 nm.) and is composed of 162 capsomeres arranged in 5:3:2 axial symmetry.

*Herpes simplex virus.*—Human herpes simplex type 1, considered the oral strain of virus, causes herpetic stomatitis, a primary disease in childhood. There is evidence that in adults acute pharyngitis is not uncommonly associated with the presence of herpes simplex virus; however, the cause-and-effect relationship is unclear. It is possible that another agent is responsible for pharyngitis in the presence of herpes simplex virus, or it is possible that disease is the result of the activation of latent herpes simplex virus.

*Epstein-Barr virus.*—Epstein-Barr virus is the cause of infectious mononucleosis, a common disease of children and young adults that is manifested by sore throat and generalized node enlargement; it is also associated with an asymptomatic infection. This agent may remain in the throat for a long time after primary infection.

*Cytomegaloviruses.*—There are two, possibly three, types of human cytomegaloviruses. These agents can be associated with pneumonitis in generalized cytomegalic inclusion disease of infancy, as well as in patients who are immunologically suppressed.

*Varicella-zoster virus.*—The varicella-zoster virus may cause pneumonia as a complication of chickenpox, particularly in adults, although it has been noted in children. These agents may also be associated with pneumonia in patients with malignancies, those on immunosuppressive drugs or those who have had organ transplants.

**LYMPHOCYTIC CHORIOMENINGITIS VIRUS.**—Infection with lymphocytic choriomeningitis virus is enzootic in mice, guinea pigs, monkeys and dogs. The most likely source of human infection is from infected house mice. The virus is 37–60 nm. in diameter, is sensitive to ether and acid and produces complement-fixing and neutralizing antibodies in convalescent persons 1–3 weeks and 6–10 weeks, respectively, after onset. Human infection is characterized by cough and sore throat, an influenza-like syndrome or severe pneumonia.

## CHLAMYDIA SPECIES

Ornithosis-psittacosis is an infection of birds that may be transmitted to man primarily by psittacine birds (parrots, parakeets, cockatoos, canaries, lovebirds and thrushes), but other birds (turkeys, ducks and chickens) may be involved. An infection in man is acquired by inhalation of dried bird excreta or by handling of feathers or tissues of infected birds. In human beings the causative agent (*Chlamydia* sp.) can readily be isolated from blood in the 1st week of illness and from sputum in the 2d week by inoculation of clinical specimens into mice, onto embryonated hens' eggs or in HeLa or monkey kidney tissue culture cells. Although the over-all incidence of human illness caused by this agent is low, infections may range from being inapparent to mild influenza-like disease to severe atypical pneumonia with appreciable mortality. The psittacosis agent is large (250–450 nm. in diameter) and an obligatory intracellular parasite. It has a complex life cycle within the infected cell, with evidence that the large (800 nm.) initial body divides by binary fission, becoming smaller and smaller. These agents are susceptible to antimicrobial drugs such as penicillin and tetracycline, are sensitive to heat, ether and acid and produce complement-fixing, agglutinating and neutralizing antibodies in the course of infection.

Psittacosis infection of man has worldwide distribution and occurs year round.

## MYCOPLASMA PNEUMONIAE

*Mycoplasma pneumoniae* (Eaton agent) cause a spectrum of illnesses ranging from inapparent infection to myringitis, with or without bullae, to a clinical syndrome known as primary atypical pneumonia associated with a rise in cold hemagglutinin titer. The agent, first isolated in 1944 by Eaton, Meiklejohn and van Herick, was believed to be a virus but has now been identified as a distinctive member of the pleuropneumonia-like group of organisms. These organisms occupy an intermediate place between viruses and bacteria, are 100–150 nm. in diameter, replicate on cell-free, semisolid or liquid mediums containing bovine heart infusion, yeast extract and horse serum and form characteristic colonies. They have no regular cell wall but only a membrane, are fragile and pleomorphic and occur in a variety of shapes, such as rings, spheres and filaments. The agent occurs commonly as a respiratory pathogen in the 5–9 year age group and the 10–20 year age group. The infection spreads slowly in a community, but intrafamilial spread is common.

*Mycoplasma pneumoniae* prevalence is cyclic in that it will occur in a community as a prolonged epidemic for 1 or 2 years and then be absent for several years. The incubation period is about 3 weeks and close contact is necessary for spread. Epidemics occur but their pattern is different from that of respiratory viruses. Although clinical

illnesses have been observed year round, the fall and early winter are periods of greatest prevalence.

## RICKETTSIAE

*Coxiella burnetii* (*Rickettsia burnetii*) is the cause of Q fever, an acute febrile illness progressing to chest pain and atypical pneumonia. This agent uses the tick as an arthropod vector and probably uses cattle, sheep, goats and small mammals as a reservoir. The incubation period is 14–26 days and the organism causes a flulike syndrome with pneumonitis in man. Unlike other rickettsial infections, Q fever is not characterized by a rash. *Coxiella burnetii* is larger than—and resists physical and chemical agents better than—certain of the other rickettsia. This microorganism withstands prolonged desiccation in dust and excreta and survives in water and milk for over 3½ years. It is an obligate, intracellular, gram-negative rod measuring approximately  $0.25 \times 0.5-1\mu$ . Infection is followed by the development of specific complement-fixing antibodies.

## PARASITES

Several parasites (Table 3) may be associated with pneumonitis in children or in adults.

**PNEUMOCYSTIS CARINII.**—*Pneumocystis carinii* is usually referred to as a protozoan, an obligate parasite; however, recent electron microscope studies suggest it may be a fungus. All efforts to propagate the agent on artificial mediums or in tissue culture have failed. The characteristic form is a cyst 8–12 $\mu$ m in diameter containing 2–8 round or oval bodies consisting of a nucleus and protoplasm; however, the microorganisms also exist as free forms.

*Pneumocystis carinii* is associated with epidemic interstitial plasma cell pneumonia in premature and debilitated infants as well as in older children and adults who are immunologically suppressed. The epidemiology of this disease is unclear, although there is some evidence there may be man-to-man spread. Passage of the parasite from

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TABLE 3.—PARASITIC DISEASES OF THE LUNGS

PARASITE	DISEASE
<i>Endamoeba histolytica</i>	Amebiasis
<i>Echinococcus granulosus</i>	Echinococcosis (hydatid disease)
<i>Paragonimus westermani</i>	Paragonimiasis
<i>Pneumocystis carinii</i>	Plasma cell pneumonia
<i>Schistosoma mansoni</i>	Schistosomiasis
<i>Toxoplasma gondii</i>	Toxoplasmosis
Larva of <i>Toxocara canis</i> and <i>Toxocara cati</i>	Visceral larva migrans (Löfller's syndrome)

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animals to man may also occur. Attempts are being made to develop effective serologic tests (complement fixation tests and fluorescent antibody tests) to aid in making the diagnosis, since special stains of specimens from open lung biopsies have been the only consistent method of identifying this agent.

**TOXOPLASMA GONDII.**—Toxoplasmosis is a widespread, usually asymptomatic, zoonotic infection caused by the ubiquitous protozoan obligate parasite *T. gondii*. These organisms vary in size and shape depending on their stage of development. Acquired toxoplasmosis may present occasionally with fever, maculopapular rash and pneumonitis (typhus-like). The parasite grows only in living cells and gives rise to antibodies that are used as an index of infection. Various serologic tests have been used to support the diagnosis of toxoplasmosis: Sabin-Feldman dye test, complement fixation test, indirect fluorescent antibody test and hemagglutination test. The epidemiology of this disease is not clear although some evidence favors spread by direct contact from various species of mammals, reptiles and birds. Raw or undercooked meat may be a source of infection, and spread may be from the feces of animals such as the cat.

**PARAGONIMUS WESTERMANI.**—Paragonimiasis, widely distributed in the Far East, is a chronic pulmonary infection of man caused by adult, hermaphroditic flukes living in cystic spaces in the lungs. *Paragonimus westermani* is a reddish brown, plump, oval fluke measuring 0.8–1.6 cm in length and 0.4–0.8 cm in width. The fluke may live 5 or 6 years, producing oval, yellow-brown ova that are coughed up in blood-stained sputum. When the ova reach a suitable water environment they hatch, producing miracidia that invade specific snails. Cercariae, subsequently produced by the snails, encyst as metacercariae in the muscles and viscera of fresh-water crustaceans, and man acquires the infection by eating these crustaceans raw or partly cooked. In the gut, larval flukes are released from the metacercariae and usually migrate from the peritoneal cavity through the diaphragm to the lung. Pulmonary lesions are resolved spontaneously in 5–10 years.

**ECHINOCOCCUS GRANULOSUS.**—Hydatid disease of the lung is prevalent in the Mediterranean and Middle Eastern countries as well as in New Zealand, Australia, South America and the Orient. Hydatid disease is caused by the ova of *E. granulosus*, a small tapeworm infesting dogs, wolves and jackals. Feces from these animals contain ova that contaminate water and vegetables ingested by sheep, cattle, hogs and humans. In the stomach, minute embryos are liberated that pass into the portal circulation, lodging primarily in the liver. Although most of the larvae reach the portal circulation, a certain percentage escape the confines of the portal bed and gain access to the systemic circulation; hematogenous dissemination to the lung occurs in up to 25% of cases. Clinical manifestations may not be

observed for as long as 10–20 years after the initial ingestion of the echinococcus eggs because cyst formation occurs so slowly.

**ENDAMOEBIA HISTOLYTICA.**—*Endamoeba histolytica* principally inhabits the cecum and colon but may also infect the lungs. The parasite, carried from the intestine to the lungs by the portal circulation, frequently starts from a nidus in a liver abscess. The parasite finds its way to the right lower lobe of the lung, sometimes using the lymphatics and thoracic duct. Pleuropulmonary amebiasis is the second most common manifestation of extraintestinal amebiasis, hepatic involvement being the most frequent.

**SCHISTOSOMA MANSONI, SCHISTOSOMA JAPONICUM AND SCHISTOSOMA HAEMATOBIIUM.**—The major sources of pulmonary disease in areas of the Middle East, Asia, Africa and Latin America are *S. mansoni*, *S. japonicum* and *S. haematobium*. After leaving the intestinal tract, the schistosome eggs hatch in water to become active miracidia that then penetrate appropriate snail species to continue the life cycle. Free-swimming cercariae eventually emerge from the snail, infect man by penetrating the skin and become larvae. The larvae gain access to the systemic circulation, pass through the lungs and eventually reach the portal and mesenteric vessels where they become adult parasites and lodge in the walls of the intestine or bladder. Although asthmatic symptoms may occur as the larvae pass through the pulmonary vasculature, the significant pulmonary involvement occurs with metastatic spread of ova (up to  $170 \times 70 \mu$  in size) produced by the adult worms; the ova cause obstruction in the pulmonary vessels as well as obliterative granulomatous arteritis after penetrating arteriole walls.

**TOXOCARA CANIS AND TOXOCARA CATI.**—The term “visceral larva migrans” was coined by Beaver and his colleagues to describe a syndrome in children characterized by eosinophilia, hyperglobulinemia, hepatomegaly and pulmonary infiltration due to nematode larvae penetrating internal organs. The causative agents are considered to be larvae of *T. canis* and *T. cati*. The life cycle of *T. canis* depends on the age and sex of the dog. Pups can be infected prenatally by larvae passing through the placenta or postnatally by ingestion of larvae or infected eggs. Larvae mature into adult worms in the upper alimentary tract (in about 3 weeks) and start laying eggs. Dormant larvae become mobile during pregnancy, migrating through the placenta into the fetus and causing prenatal infection. Once the bitch is infected she is probably capable of passing the infection on to several litters of puppies. When infective eggs of toxocara are swallowed by a human being, they hatch in the upper alimentary tract and the larvae enter the portal system, reaching the liver. The ova have thick shells and are quite resistant to adverse conditions. Some of the larvae migrate from the liver to the lung and to the heart, where they reach the systemic circulation. Pulmonary involvement is common with this infection. Visceral larva migrans occurs mainly in young children.

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TABLE 4.—FUNGAL DISEASES OF THE LUNG

FUNGUS	DISEASE
<i>Actinomyces bovis</i>	Actinomycosis
<i>Aspergillus niger</i>	Aspergillosis
<i>Blastomyces dermatitidis</i>	Blastomycosis
<i>Candida albicans</i>	Candidiasis
<i>Coccidioides immitis</i>	Coccidioidomycosis
<i>Cryptococcus neoformans</i>	Cryptococcosis (torulosis)
<i>Histoplasma capsulatum</i>	Histoplasmosis
<i>Mucor absidia</i>	Mucormycosis
<i>Nocardia asteroides</i>	Nocardiosis

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## FUNGI

Most pulmonary infections due to a fungus occur sporadically and have worldwide distribution. Certain geographic areas of the world have a higher incidence of fungi and subsequently a higher prevalence of disease. Males are more frequently infected with fungal diseases than females. The prolonged use of broad-spectrum antibiotics, steroid therapy and anticancer drugs may contribute to whether or not a fungal infection becomes symptomatic, causing clinical disease. An increased susceptibility to cryptococcosis and histoplasmosis has been observed in patients with malignant diseases of the reticuloendothelial system, whereas a high incidence of mucormycosis is associated with uncontrolled diabetes mellitus.

Clinical manifestations of fungus infections are similar to those associated with tuberculosis. Disease is characterized by slow evolution of chronic infection that persists for months and even years. If pathologic specimens are examined, granulomatous lesions may be found. Complement-fixing, precipitin and agglutinin antibodies develop as a result of mycotic infections and, along with cultures, aid in diagnosis. Since descriptions of the fungi causing disease are intimately related to the clinical syndromes they cause, the individual fungi will be discussed with the clinical syndromes; however, Table 4 lists the clinically important respiratory fungus infections.

## BACTERIA

Since the vast majority of respiratory infections are caused by viruses, the role of bacteria as a cause of acute respiratory tract disease is unclear, but their importance should not be negated. The differential diagnosis between viral and nonviral respiratory illness is usually made on clinical grounds, including "response to therapy," rather than on specific information from viral or bacterial cultures. It would appear that bacteria are of considerable importance in both primary and secondary infections in acute respiratory illnesses.

**HEMOLYTIC STREPTOCOCCUS.**—The group A  $\beta$ -hemolytic strepto-

cocci are responsible for multiple infections in childhood and are perhaps the most significant bacterial cause of upper respiratory infections. The type of infection elicited depends on the particular strain of group A hemolytic streptococci present, the portal of entry and certain host factors such as age and immunity.

These microorganisms are characterized by the fact that they grow in chains, have capsules that are primarily composed of hyaluronic acid and are temperature dependent for optimal growth. The major component of the bacterial cell wall is group A carbohydrate and the most important surface protein is the M protein, which plays an important role in virulence. Group A hemolytic streptococci also contain streptokinase, deoxyribonuclease, streptolysins S and O, hyaluronidase and erythrogenic toxin. When any of these substances are elaborated, the production of specific antibodies for the substance follows, and measurement of the level of these antibodies may be used as an aid to diagnosis. People of all ages, both sexes and all races are susceptible to streptococcal infections and the geographic distribution appears to be related to climate.

**STAPHYLOCOCCUS.**—As respiratory tract pathogens, the primary significance of staphylococci is in causing severe pneumonia, especially in infants. Staphylococci, named from a Greek word meaning "bunch of grapes," are gram-positive cocci occurring in clusters. *Staphylococcus aureus* may be found as a normal inhabitant of the skin and mucous membranes. Although there seems to be a significant correlation between coagulase (an extracellular enzyme) formation and virulence of staphylococci for man, the role of coagulase in the pathogenesis of human infections is unknown. Although many strains of staphylococci that form coagulase also give rise to an exotoxin capable of producing tissue necrosis or death in animals and hemolysis of rabbit erythrocytes, the part played by exotoxin in the pathogenesis of disease is unknown. Some strains of coagulase-positive staphylococci of phage group II may elaborate an exfoliative toxin. Staphylococci multiply locally in tissue and produce hyaluronidase, which increases the permeability of connective tissue and probably serves to promote the spread of these organisms.

Severe nutritional deficiencies, diseases such as diabetes mellitus, unhygienic surroundings and overactivity of sebaceous glands are some of the host factors that may interfere with native resistance and promote an increased incidence of staphylococcal infections.

**PNEUMOCOCCUS.**—Before the antibiotic era the pneumococcus organism was primarily or secondarily responsible for most pneumonias in children and adults. With the extensive use of sulfonamides, penicillins and other antimicrobial agents, the diagnosis of pneumococcal pneumonia is seldom made. *Streptococcus pneumoniae* in its virulent form is composed of a gram-positive, lancet-shaped cell (somatic portion) surrounded by a polysaccharide capsule that is specific for each serologic type. The capsule acts as protection against phagocyto-

sis and is significantly associated with virulence of the organism. At least 75 different serologic types of pneumococci have been described; the most frequent types encountered in adults with pneumonia are types I-IV and types VII-X. In infants, type XIV is most common and in children, types I, V and VII are. Pneumococcus type III and pneumococci of the higher types are common inhabitants of the normal upper respiratory tract.

**HAEMOPHILUS INFLUENZAE.**—Virulent *H. influenzae*, which are gram-negative pleomorphic rods, have a type-specific capsular polysaccharide; six distinct types—a through f—may be identified by quellung reaction, precipitin tests or agglutination tests. Perhaps the most important role played by *H. influenzae* as agents of respiratory disease is their implication as a secondary bacterial invader in epidemic influenza, pathogenic for all ages. As a primary pathogen, *H. influenzae* infects infants and children, giving rise to a variety of respiratory tract syndromes. *Haemophilus influenzae* type b organisms are responsible for over 90% of clinically significant haemophilus infections in infants and children. Nonencapsulated, nontypable *H. influenzae* organisms are frequently isolated from the nasopharynx of normal children and adults; the significance of this is unknown.

**BORDETELLA PERTUSSIS.**—*Bordetella pertussis* causes whooping cough. In the catarrhal stage of disease the manifestations are those of an upper respiratory tract infection, without the true cause being suspected. This organism is a small gram-negative, nonmotile rod with specific growth requirements and is best isolated on Bordet-Gengou mediums from nasopharyngeal specimens taken during the first 2 weeks of illness. This infection is worldwide in distribution with no place, race or nationality being exempt. Seasonal concentrations of instances of whooping cough are less marked than with many other common contagious diseases of childhood; however, there may be a rise in incidence in the spring and summer. Little or no immunity is transferred from mother to newborn infant. In contrast with experience with other infectious diseases, the morbidity and mortality of pertussis are higher for females than for males.

**CORYNEBACTERIUM DIPHTHERIAE.**—Klebs discovered the diphtheria bacillus in 1883, and its etiologic relationship to disease was demonstrated in 1884. *Corynebacterium diphtheriae* organisms are gram-positive rods that vary in diameter and have ends that are broader than the center, causing a typical club-shaped appearance. The protoplasm may be irregularly distributed in the cells, producing a beaded or bandlike appearance in some organisms. The most important characteristic of the three types of *C. diphtheriae* is an ability to produce an exotoxin, both in vivo and in vitro, which is responsible for the serious clinical manifestations of diphtheria, an acute infectious preventable disease. The toxin is unstable and is destroyed by heat, light and aging. Virulent diphtheria bacilli lodge in the nasopharynx of susceptible persons, grow and elaborate the toxin, and this exotoxin is



absorbed by the local mucous membranes. The toxic effect on the cells causes tissue necrosis, which supports further growth of the organism and production of more toxin. A vicious cycle ensues with more and more tissue being destroyed. The size of the membrane usually reflects the amount of toxin produced: the larger the membrane, the more toxin is available for absorption. Diphtheria toxin is distributed via the blood stream to tissues all over the body. Whereas it may have a damaging effect on almost any tissue, the toxin has a predilection for heart muscle and nervous tissue.

**OTHER GRAM-NEGATIVE BACILLI.**—Lower respiratory infections caused by *E. coli*, pseudomonas species, proteus species and bacteroides species have been increasing, primarily in middle-aged and elderly men who have predisposing conditions such as heart trouble, pulmonary disease, diabetes mellitus, gastrointestinal infection or alcoholism, as well as in patients who are immunologically suppressed. Hospitalizations are usually prolonged and management difficult.

## PATHOGENESIS AND DIAGNOSTIC STUDIES

### FACTORS IN PATHOGENESIS

Many factors interact to determine when an infection will occur, the course it will take and its outcome. The characteristics of the specific infectious agent, along with the previous experience of the host with it, are the most important determinants of whether or not respiratory infection will occur.

Some viruses have a cytolytic effect and destroy the cell in which they multiply whereas others multiply within the cell with little or no cellular damage. The presence of an asymptomatic viral infection that is interferon-producing may prevent or abort infection with another virus. Serum antibody and secretory antibody interact to protect the person against some viral infections.

Mycoplasma organisms are probably adsorbed to epithelial cells and deliver a "toxin" to the cell, at times destroying ciliated epithelial cells.

In bacterial infections, the normal flora of the patient is probably important in determining whether or not symptomatic infection will occur with the introduction of a new agent. The ciliary activity of cells, their ability to phagocytize and delayed hypersensitivity are other factors that may be important. Secondary bacterial infections probably occur when cells, damaged by a primary viral infection, become a good medium for bacterial growth and ciliary damage allows the spread of bacteria to lower respiratory sites.

Important factors in the epidemiology of respiratory infections include: exposure, season of the year, appropriate incubation period, age of the patient, previous respiratory illnesses, sex and socio-economic factors.

## ROLE OF ALLERGY

Anecdotal information would indicate that "allergic children" suffer with more viral infections than do nonallergic children; however, there are no convincing data that such is the case. Susceptible allergic and nonallergic children should be infected at the same rate. Some reports in the literature indicate that wheezing occurs more often during viral respiratory illnesses in allergic than in nonallergic children; however, other reports indicate that viral infections, even when accompanied by upper respiratory illness, do not precipitate asthmatic attacks. It is most likely that many of the so-called colds that occur in allergic children do not result from viral infection but are primarily allergic manifestations.

## LEUKOCYTE COUNT

In general, clinicians have associated leukocytosis and a "shift to the left" with a bacterial respiratory illness and have associated leukopenia with a relative lymphocytosis with a viral respiratory illness. Studies by Nichol and Cherry, Portnoy and colleagues and Douglas and colleagues would contradict this assumption, for these investigators found that an increase in white blood cell counts and an increased percentage of polymorphonuclear leukocytes correlates best with inflammation regardless of the infectious etiology. These studies would indicate that a white blood cell count and differential count do not differentiate viral from bacterial respiratory illness.

## PROCEDURES YIELDING SPECIMENS FOR LABORATORY EXAMINATION

Accurate etiologic diagnosis is essential to appropriately treat lower respiratory infections. Collecting specimens from the lower respiratory tract for examination becomes a difficult maneuver. Secretions from the lungs, the bronchi or the trachea pass through the pharynx and the mouth, which invariably contain so-called normal flora and virtually assure some nonspecific growth on culture. Appropriate specimens may be obtained from the lower respiratory tract by an approach via the upper respiratory tract or via extrapulmonary means.

Upper respiratory tract approaches include obtaining specimens by expectoration, tracheal suction and bronchoscopy, whereas extrapulmonary approaches include lung biopsy, lung tap with aspiration or transtracheal aspiration. The number of bacteria ordinarily present in the nasal and oral regions is impressive (see Table 5). Staphylococcus species are common in the nose, whereas aerobic and anaerobic streptococci and nonpathogenic neisseria species are predominant organisms in the oropharynx. Frequently, certain potentially pathogenic bacteria such as *S. aureus*, hemolytic streptococcus, *S. pneumoniae* and *H. influenzae* may also be found in the oropharynx but

TABLE 5.—NUMBER OF BACTERIA USUALLY  
PRESENT IN NASOPHARYNX\*

LOCATION	NO. PER ML	
	Aerobic	Anaerobic
Nose	10–10 <sup>4</sup>	10 <sup>2</sup> –10 <sup>5</sup>
Saliva	10 <sup>7</sup> –10 <sup>8</sup>	10 <sup>8</sup> –10 <sup>9</sup>
Tooth surfaces	10 <sup>5</sup>	10 <sup>6</sup>
Gingiva	10 <sup>7</sup>	10 <sup>7</sup>

\*Modified from Hoeprich, P. D.: Etiologic Diagnosis of Lower Respiratory Infections, Calif. Med. 112:2, 1970.

not cause disease. Gram-negative bacilli, *S. aureus* and *Candida albicans* may predominate after antibiotic therapy.

**EXPECTORATION.**—The production of a sputum specimen by expectoration is usually associated with a number of bacteria resident in the upper respiratory tract. Lapinski and colleagues have suggested that serial, threefold washings of a small quantity of sputum might be effective in removing organisms picked up in the upper respiratory tract. Although washing of sputum is effective, because it is a cumbersome technic, it has not gained general acceptance.

**TRACHEAL SUCTION.**—The use of tracheal suction, that is, the passage of a catheter through the nose or throat into the trachea for the purpose of aspirating a specimen, can be associated with misinformation. Organisms from the oropharynx might be aspirated into the trachea in the process of obtaining a specimen, and the passage of the catheter through the contaminated oropharynx and larynx will most likely contaminate the tracheal specimen.

**BRONCHOSCOPY.**—Bronchoscopy is associated with contamination by oropharyngeal organisms as the instrument is passed through the anesthetized upper respiratory tract into the lower respiratory tract. Material aspirated through the bronchoscope might easily be seeded with potentially pathogenic microorganisms that originate in the upper respiratory tract. Local anesthetics (lidocaine and tetracaine) that are used to permit bronchoscopy inhibit the growth of non-acid-fast and acid-fast bacteria as well as fungi, and this factor has been associated with spurious culture results obtained at bronchoscopy.

**BIOPSY SPECIMENS.**—The advantages of a biopsy specimen include: (1) absence of contaminating microorganisms from the upper respiratory tract, (2) assurance of the source of the specimen and (3) accurate culture results since it is generally accepted that the lower respiratory tract is normally sterile. The two technics for obtaining biopsy specimens include cutting-needle excision and open chest surgical biopsy. Neither technic yields a high percentage of culture information and both are associated with pneumothorax and hemorrhage. The advantage of the open chest biopsy is that the surgeon can select

TABLE 6.—COMPARISON OF VARIOUS METHODS FOR SECURING SPECIMENS OF LOWER RESPIRATORY TRACT SECRETIONS AND EXUDATES\*

METHOD	No. OF PROCEDURES	YEARS OF STUDIES	MORTALITY	MORBIDITY	POTENTIAL PATHOGENS
Washed sputum	408	1964-67	0	0	217 (53.2%)
Bronchoscopy	530	1943-58	0	0	395 (74.5%)
Biopsy:					
Cutting needle	487	1960-67	1 (0.2%)	84 (17.3%)	Infrequent
Open chest	441	1949-64	7 (1.6%)	>59 (>13.4%)	Infrequent
Aspiration:					
Diffuse disease	~2,189	1911-65	?	?	~912 (~41.6%)
Localized lesions	754	1939-67	3 (0.4%)	89 (4.8%)	<50 (<6.6%)
Transtacheal	305	1963-68	0	1 (0.3%)	173 (56.7%)

\*From Hoeprich, P. D.: Etiologic Diagnosis of Lower Respiratory Tract Infections, Calif. Med. 112:1, 1970.

TABLE 7.—RECOMMENDED DIAGNOSTIC PROCEDURES\*

Virus	ISOLATION SPECIMENT										RECOMMENDED SEROLOGIC TEST (PAIRED SERUMS)						
	CSF	STL	TS	BLD	VF	TIS	Urine	SAL	SPU	HIST	NEUT	HAI	CF	FA	CA	ST-MG	HDI
Adenovirus		X	X			Tonsil, lung					X	X	X				
Arbovirus	X		X	X		CNS					X	X	X				
Cytomegalovirus						Misc.	X†	X		X	X	X	X	X			
Mycoplasma pneumoniae			X			Lung			X		X <sup>f</sup>	X	X	X	X	X	
Enterovirus		X	X			CNS					X	X†	X\$				
Exanthems:																	
Rubeola			X	X		Lung					X	X	X				X
Rubella		X	X	X							X	X	X	X			
Herpes varicellae			X		X	Misc.			X	X	X	X	X				X
Herpes hominis	X		X		X	Misc.			X	X	X	X	X				X
Vaccinia			X		X				X	X	X	X	X				X
Variola				X	X			X			X	X	X				X

Lymphocytic choriomeningitis (LCM)	X	X	X	X	X	X	X	X
Myxovirus:								
Influenza		X					X	X
Parainfluenza		X		Lung			X	X
Mumps	X	X		Lung	X		X	X
Psittacosis (Bedsonia)		X		Misc.	X		X	X
Reovirus		X		Misc.	X		X	X
Respiratory syncytial		X				X	X	X
Rhinovirus		X		Lung		X	X	X

CSF = cerebrospinal fluid  
 STL = stool (or rectal swab)  
 TS = throat swab  
 BLD = whole, clotted blood  
 VF = vesicular fluid

TIS = tissue  
 SAL = saliva  
 SPU = sputum  
 HIST = histologic procedures  
 NEUT = neutralization  
 HAI = hemagglutination inhibition

CF = complement fixation  
 FA = fluorescent antibody  
 CA = cold agglutinins  
 ST-MG = strcp-MG  
 HDI = hemadsorption inhibition  
 CNS = central nervous system

\*From Portnoy, B.; Pediatric Virology, Calif. Med. 102:434, 1965. (Updated by personal communication with Doctor Portnoy.)

†Not useful for all enteroviruses.  
 ‡Fresh, refrigerated; do not freeze.  
 §Late convalescent serum necessary.  
 ¶Metabolic inhibition test.  
 ||Crosses with lymphogranuloma venereum.

grossly diseased lung tissue as well as appropriate parietal pleura and lymph nodes for examination. A portion of each biopsy specimen should be submitted for routine, acid-fast, anaerobic and fungal cultures. Although the technics of bronchial brushing and mediastinoscopy have been useful in acquiring etiologic information relative to malignancies, their usefulness for purposes of identifying etiologic agents of respiratory infections is limited.

**LUNG TAP (ASPIRATION).**—Aspiration technics to diagnose lung disease by inserting a needle percutaneously through the chest wall have been used since 1883. More recently, Bandt *et al.* have used fluoroscopic guidance of the aspiration needle to suspected localized pulmonary infections, especially in patients with other serious illnesses. Pneumothorax and hemoptysis represent associated but acceptable morbidity with this technic when compared with the risks of open biopsy (1.6% mortality) or empiric therapy (no definite diagnosis).

Percutaneous entry into the trachea (transtracheal aspiration) provides yet another access to the lower respiratory tract that bypasses the upper respiratory tract. This technic compares favorably with other technics in searching for an etiologic diagnosis of lower respiratory tract infections (Table 6) and should be considered when there is no clear predominance of one potential pathogen in the sputum, when there is doubt as to the validity of a predominant pathogen in sputum cultures, when sputum is not available and when there is concern that superinfection may have intervened in the lower respiratory tract. Transtracheal aspiration is a bedside procedure and serious complications are uncommon.

**LABORATORY PROCEDURES.**—In certain situations, the effort should be made to obtain viral studies. Appropriate specimens for bacteriology studies would include throat swabbings, nasopharyngeal swabbings, sputum, blood and other specimens obtained via special procedures, i.e., fluid from pleural effusion. Mycoplasma cultures are available in a limited number of institutions or through County or State laboratories. Viral diagnostic studies are available in special institutions or through County or State laboratories. Serologic tests would include complement fixation tests, hemagglutination inhibition tests, neutralization titers, indirect immunofluorescent antibody tests and hemadsorption inhibition tests. Table 7 lists appropriate viral diagnostic procedures for consideration.

## CLINICAL SYNDROMES

In general, illness is classified according to the organ system primarily affected, and an infectious etiology can frequently be associated with a specific agent. With respiratory illnesses this is not the case, since illness may be very extensive, may involve several organs in sequence or concurrently, may be associated with multiple agents and may give rise to one of several clinical pictures. The most common

syndromes associated with upper respiratory infections, infections causing airway obstruction, infections involving the upper and lower respiratory tract and lower respiratory infections can be briefly characterized. The etiologic agents associated with these syndromes are listed in Table 8.

## UPPER RESPIRATORY INFECTIONS

**ACUTE OTITIS MEDIA.**—Acute otitis media has been described as inflammation in the middle ear causing redness and fullness or bulging of the ear drum with pain. Otitis media may be present without fever and without a history of ear pain or pulling on the ear. Although the bacterial etiology of otitis media is well established (pneumococcus, *H. influenzae* and hemolytic streptococcus), viruses, mycoplasma and L-forms also play a significant role in etiology. Some studies have demonstrated dual infections (virus and bacteria) of the middle ear. This condition may occur when a viral infection causes primary damage followed by a bacterial infection. Since 50% or more cases of otitis media are associated with bacteria, all patients with this disease should be treated with appropriate antibiotics. If the ear is draining, or if a myringotomy is done, a gram stain of the material obtained may be helpful in identifying an organism and deciding on specific therapy.

A follow-up visit in 10 days to 2 weeks is indicated for both non-draining and draining otitis media since the duration of therapy is usually determined by the appearance of the tympanic membrane. If drainage is still present or if the tympanic membrane persists in looking abnormal, with a bulging pars tensa and pars flaccida, then it is the policy of this author to refer the patient to an otolaryngologist. Antibiotic therapy is appropriately selected depending on the age of the patient and the suspected etiology of the infection.

**ACUTE SINUSITIS.**—Sinusitis is an acute infection of one or more of the paranasal sinuses and occurs when some alteration of the nasal mucous membrane has taken place. The paranasal sinuses are directly contiguous to and communicate with the upper respiratory tract; therefore, acute viral respiratory disease, allergic rhinitis, foreign bodies, deviation of the nasal septum and enlarged adenoids may obstruct the ostia of the sinuses, followed by bacterial invasion and acute infection. Although sinusitis is common, there are no exact data regarding frequency of occurrence. Fever, pain, tenderness and swelling over the involved sinus, the usual indication of sinusitis in the adult, is not usually present in the child (Fig. 1). The child may have a profuse mucopurulent discharge from one or both nostrils, a cough, particularly at night, and a diffusely red pharynx with a clinging, thick, mucopurulent discharge. The organisms most frequently responsible for sinusitis in the adult are *S. aureus*, hemolytic streptococcus, pneumococcus, *H. influenzae* and anaerobic organisms. Therapy should con-



TABLE 8.—ETIOLOGY OF ACUTE RESPIRATORY INFECTIONS

CLINICAL SYNDROMES	ETIOLOGY		Other
	Common Viruses	Common Bacteria	
Upper Respiratory Infections Acute otitis media	Parainfluenza, respiratory syncytial virus (RSV), Coxsackie viruses	Pneumococcus, <i>H. influenzae</i> , hemolytic streptococcus	<i>Mycoplasma pneumoniae</i>
Acute sinusitis	Probably most respiratory viruses	Staphylococcus, pneumococcus, hemolytic streptococcus, <i>H. influenzae</i> , anaerobes	
Pharyngoconjunctival fever	Adenoviruses, influenza, Coxsackie viruses, ECHO viruses, rhinoviruses		
Acute tonsillopharyngitis with ulcers or vesicles	Herpes simplex, Coxsackie viruses, ECHO viruses		
with exudate or membrane	Adenoviruses, Epstein-Barr virus (EB virus)	Hemolytic streptococcus, <i>Corynebacterium diphtheriae</i>	<i>M. pneumoniae</i>
without ulcers, vesicles, exudate, membrane	Adenoviruses, parainfluenza, RSV, Coxsackie viruses	Hemolytic streptococcus	
Common cold	Adenoviruses, parainfluenza, RSV, rhinoviruses, coronavirus, ECHO viruses, Coxsackie viruses, reoviruses, influenza	<i>H. influenzae</i> , <i>Bordetella pertussis</i>	<i>M. pneumoniae</i>
Infections Causing Airway Obstruction			
Croup syndrome	Same as laryngotracheitis	<i>H. influenzae</i> , type b	
Acute epiglottitis			
Acute laryngitis			

Acute laryngotracheitis, with/without bronchitis	Rhinoviruses, parainfluenza, adenoviruses, influenza, RSV, ECHO viruses (Coe virus)	<i>H. influenzae</i> , <i>C. diphtheriae</i>	<i>M. pneumoniae</i>
Acute bronchitis	Same as laryngotracheitis	<i>H. influenzae</i>	<i>M. pneumoniae</i>
Acute bronchiolitis	RSV, adenoviruses, parainfluenza, influenza, rhinoviruses	<i>C. diphtheriae</i>	
Diphtheria			
Upper-Lower Respiratory Infections			
Influenza	Influenza, parainfluenza, adenoviruses, Coxsackie viruses, echoviruses, lymphocytic choriomeningitis (LCM)		
Pertussis	Adenoviruses	<i>B. pertussis</i> , <i>Bordetella parapertussis</i>	
Lower Respiratory Infections			
Acute pneumonitis	Adenoviruses, varicella, rubeola, herpes simplex, parainfluenza, RSV, LCM, human cytomegalovirus	Pneumococcus, staphylococcus, hemolytic streptococcus, <i>H. influenzae</i> , anaerobes, gram-negative rods, <i>Mycobacterium tuberculosis</i> , atypical mycobacteria	Chlamydia species, <i>Pneumocystis carinii</i> , <i>Toxoplasma gondii</i> , <i>Coxiella burnetii</i> , <i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i> , <i>M. pneumoniae</i> , <i>Actinomyces israelii</i>
Necrotizing pneumonia		Anaerobic organisms (bacteroides, fusobacterium), staphylococcus, klebsiella, pseudomonas, <i>Escherichia coli</i>	
Empyema		Same as for necrotizing pneumonia	<i>A. israelii</i> , <i>Nocardia asteroides</i>

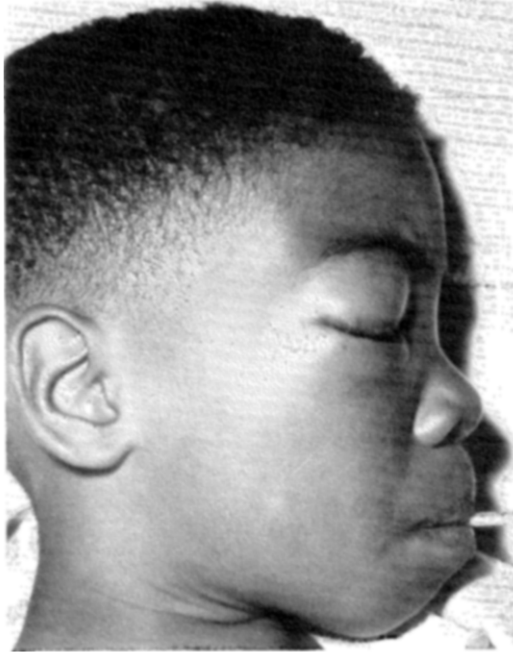


FIG. 1.—Boy, aged 8½ years, with fever and headache as well as erythema, pain and edema surrounding the right eye and right side of the face. Roentgenograms show pansinusitis.

sist of symptomatic treatment, including codeine for severe pain, the use of moist heat over the affected sinuses and nose drops with a vasoconstrictor to promote drainage. Systemic antibiotics may be indicated and should be selected according to the etiologic agent suspected.

**PHARYNGOCONJUNCTIVAL FEVER.**—Bell and others describe this illness as an epidemic disease of children living together in close contact. It is characterized by fever, an acute pharyngitis with an exudate, cervical adenopathy and conjunctivitis with follicle formation that may be unilateral or bilateral. Adenoviruses, influenza viruses and enteroviruses have been associated with this syndrome.

**ACUTE TONSILLOPHARYNGITIS.**—Tonsillopharyngitis may present with or without an exudate, a membrane, vesicles or ulcers. Patients who have none of these usually have either a viral or hemolytic streptococcal sore throat with fever and headache. The tonsils and pharynx are usually injected and edematous; frequently cervical adenitis is present.

Acute tonsillopharyngitis presenting with an exudate or membrane is most likely caused by hemolytic streptococcus, especially in older children. However, adenoviruses, Epstein-Barr virus (infectious mononucleosis), *Corynebacterium diphtheriae* and perhaps *M. hominis* can be associated with an exudative pharyngitis. If nothing in the history

or physical examination suggests diphtheria, if symptoms have been present for less than 4 days, if there is no chronic disease and if the parents are reliable, antibiotic therapy can be delayed until the results of the throat culture are known. If the throat culture is negative for hemolytic streptococci, no antibiotic treatment is required. If the culture is positive for hemolytic streptococci, then treatment must be instituted and throat cultures should be obtained on other members of the family.

Acute tonsillopharyngitis manifested by vesicles or ulcers is most frequently caused by Coxsackie viruses group A or herpes simplex virus. Herpangina is a clinical syndrome usually related to Coxsackie viruses group A and characterized by fever and papular, vesicular and ulcerative lesions on the anterior tonsillar pillars, soft palate, tonsils, pharyngeal mucous membrane and posterior part of the buccal mucosa.

Primary herpetic stomatitis is a disease of infancy and early childhood with manifestations of fever, pain in the mouth and salivation. On physical examination there are vesicular and ulcerative lesions, as well as erythema and edema, on the labial and buccal mucosa, tongue and gingiva. Cervical adenitis is usually present. Antibiotics have no value in the treatment of these infections unless they become secondarily infected.

**COMMON COLD, FEBRILE NASOPHARYNGITIS OR ACUTE RESPIRATORY DISEASE.**—"The common cold," "febrile nasopharyngitis," "ARD," "upper respiratory infection" and "coryza" are all terms that have been used to designate the most frequent and recurrent of man's illnesses. The common cold is costly; economic losses have been estimated at more than \$2,000,000,000 annually. Colds account for more than one fourth of the acute illnesses and some 287,000,000 days annually of restricted activity. Estimates of the number of colds experienced annually in the United States range from 117,000,000 reported officially to 500,000,000. For symptomatic relief, Americans spend \$400,000,000 a year on products whose benefits are doubtful.

The common cold, spread by person-to-person contact, is worldwide in distribution. Neither humidity nor atmospheric pollutants have been proved to activate latent respiratory viruses to cause colds, which contradicts the common belief that cold weather may "cause a cold." Adenoviruses, influenza and parainfluenza viruses, respiratory syncytial virus, a few ECHO and Coxsackie viruses, coronaviruses and rhinoviruses probably account for over half of the colds in adults. Hemolytic streptococci may account for an additional 5-10%. Coronaviruses probably are second only to rhinoviruses as important causes of the common cold; viruses not yet identified will most likely be added to the list of cold-producers in the future. The annual peak of colds in September and October is produced primarily by rhinoviruses.

An extremely small amount of virus will infect 95% of the popula-

tion in volunteer studies, suggesting that natural infection probably occurs with small doses of virus. The incubation period is short, with an average length of about 2 days.

The common cold is characterized by slight to no fever, nasal congestion and thin, clear, watery, profuse nasal discharge, conjunctivitis, sore throat, cough and infection of the pharynx and tonsils without exudate or membrane. Swelling of the nasal mucosa soon blocks one or both nostrils and sneezing attacks are frequent. The eyes water and headache or a feeling of "fullness in the head" is common. Febrile nasopharyngitis in infants may occasionally be caused by hemolytic streptococcus; therefore, nasopharyngeal cultures should be obtained.

Physical examination shows inflamed and swollen nasal and pharyngeal mucous membranes with occluded nasal passages. The patient complains of impairment of smell and hearing. Uncomplicated colds seldom last more than 3 or 4 days.

Secondary bacterial infections such as otitis media, tonsillitis, sinusitis, cervical adenitis, laryngitis, bronchitis, bronchiolitis and pneumonia may develop.

Treatment of colds is symptomatic and supportive with aspirin and oral fluid therapy. The use of phenylephrine or oxymetazoline nose drops to shrink the nasal mucosa and prevent middle ear infections is of questionable therapeutic value but may bring symptomatic relief. Nose drops may be indicated for infants before feeding or at bedtime, but their effect is transitory. Bed rest is recommended to reduce the patient's chances of spreading infection to others or acquiring a secondary bacterial infection himself. There is no effective method of preventing or controlling an infection with the common cold unless it is good hygiene on the part of the patient and his contacts. Throat lozenges without antimicrobial agents may help to relieve the sore throat, and if the cough becomes bothersome, a cough syrup with or without codeine may bring some relief. Although much has been written about the value of large doses of ascorbic acid (vitamin C) to prevent the "common cold," absolutely convincing data from controlled studies are still not available. Antibiotics have no place in the primary management of acute viral respiratory disease and the use of prophylactic antibiotics to prevent secondary bacterial infection not only fails to do this but may result in the alteration of normal bacterial flora and the establishment of resistant organisms.

## INFECTIONS CAUSING AIRWAY OBSTRUCTION

**CROUP SYNDROME.**—Epiglottitis, laryngitis and laryngotracheitis, with or without bronchitis, are acute inflammatory diseases that are usually caused by infectious agents, cause obstruction of the airway passages and produce the characteristic clinical picture designated as "croup." The precise anatomic localization of the site of inflammation in the airway is not only difficult but usually unnecessary, since all

structures are usually involved and the primary concern is to relieve obstruction of the airway.

Acute epiglottitis is characterized by a sudden onset of fever, barking cough, drooling due to pain on swallowing, hoarseness and respiratory distress. Physical examination reveals inspiratory stridor and a bright-red, swollen epiglottis. A lateral x-ray of the neck will show the enlarged, boggy epiglottis, and this is perhaps the safest way to make the diagnosis (Fig. 2). The illness progresses rapidly to severe prostration and death within 24 hours unless appropriate supportive care and antibiotic therapy is instituted. A tracheostomy may be life-saving. *Haemophilus influenzae* type b organisms are usually isolated from the nose, throat and blood.

Acute laryngitis begins with hoarseness and a croupy cough that may be worse at night. Mild fever, anorexia and malaise may be the only constitutional signs until the inflammation progresses rapidly to the stage of obstruction occurring below the vocal cords where the soft, subglottic tissues become red and injected, swollen and edematous and meet in the midline. A mucopurulent exudate may be present, adding to obstruction of the airway; the epiglottis is usually normal. Hoarseness becomes more marked and breathing becomes labored, with inspiratory stridor and inspiratory retraction of the suprasternal notch, supraclavicular spaces, substernal region and even intercostal spaces. The child grows restless and agitated because of air hunger and may become cyanotic and exhausted if the obstruction is unrelieved.

The infection may descend rapidly to become laryngotracheitis,

FIG. 2.—Boy, aged 4, admitted with stridor and a beefy-red, swollen epiglottis on physical examination. Lateral neck x-ray, diagnostic of epiglottitis, shows the swollen epiglottis (arrow).



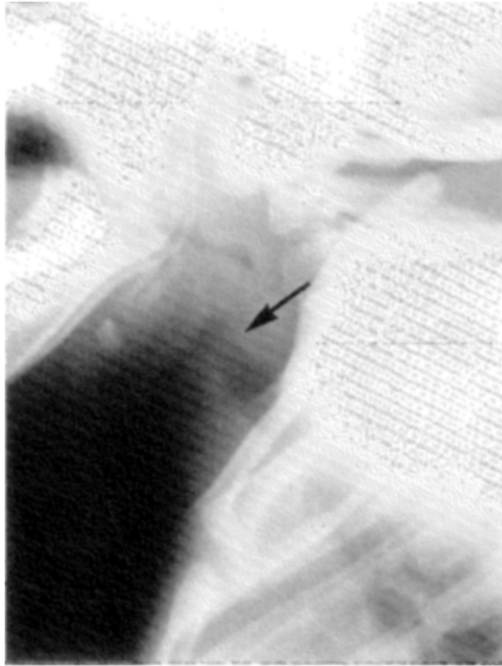


FIG. 3.—Boy, aged 2, admitted with stridor and a normal epiglottis on physical examination. Lateral neck x-ray shows narrowing of the trachea (*arrow*) which is compatible with croup.

usually associated with fever, cough and a progression of all symptoms.

With further extension of the inflammation and the development of laryngotracheobronchitis (Fig. 3), the patient struggles for air and becomes more prostrate; an expiratory wheeze and rales then are heard on auscultation of the chest. If a mainstem bronchus becomes plugged with the thick mucoid exudate, air hunger, cyanosis, apprehension and restlessness are increased, and the heart and mediastinum may be shifted. Relief from the severe dyspnea occurs after the plugged bronchus has been aspirated.

A serious complication in the course of laryngotracheobronchitis is the formation of crusted exudate in the tracheobronchial tree, probably from breathing air that is not saturated with moisture and because of the temporary cessation of function of the mucus-secreting glands of the respiratory tract. This crusted exudate may cause obstruction that leads to collapse of a segment of lung with a loss of the cough reflex and an increase in cyanosis.

Mediastinal emphysema, pneumothorax and bronchopneumonia are other common complications as the disease process extends to the terminal bronchioles and alveoli.

Spasmodic croup, which is not infectious, is distinguished by an absence or mildness of signs of inflammation, typical remissions during the daytime and a past history of similar attacks with uneventful recovery. Foreign bodies, retropharyngeal abscesses and angioneurotic edema characterized by supraglottic swelling at times all present like croup.

The key to successful treatment of croup is to maintain the airway and to combat infection. The patient responds best in an atmosphere with a high humidity level. Supportive care includes rest and plenty of fluids. Sedatives, opiates and ephedrine are contraindicated and expectorants bring little relief. In many cases a period of rest, breathing of humidified air and supportive treatment are associated with gradual improvement and complete recovery.

If the patient demonstrates increasing respiratory distress and restlessness even though he is in an atmosphere of high humidity and high oxygen levels, then the increasing obstruction to the airway makes a tracheostomy mandatory. The establishment of an airway results in immediate relief. After a tracheostomy tube has been placed, frequent aspiration of the tracheobronchial secretions is necessary to prevent plugging.

The use of corticosteroid therapy as an anti-inflammatory agent to reduce edema and improve the airway is based on anecdotal data rather than scientific fact. Extensive studies on laboratory animals supported by clinical experience indicate that cortisone and adrenocorticotrophic hormone enhance susceptibility to infection rather than produce an anti-inflammatory effect. Nevertheless, some patients appear to improve with corticosteroid therapy and the responsible physician must consider the relative merits and risks of therapy in making a decision for a particular patient.

The use of nebulized racemic epinephrine has become popular in the therapy of croup because uncontrolled trials indicate good responses; however, Gardner and colleagues, in a double-blind controlled study, showed that good results can be obtained with the nebulization of saline as well as racemic epinephrine. It would appear that there is presently no valid indication for the use of racemic epinephrine in the therapy of croup.

Since most cases of infectious croup are viral in origin, the indications for antibiotics are limited to those cases caused by *H. influenzae* type b and *C. diphtheriae*.

**ACUTE BRONCHITIS.**—As a primary disease, acute bronchitis is rare. Bronchitis usually occurs with inflammation of the trachea; therefore, the term “tracheobronchitis” is probably more accurate. An upper respiratory tract infection usually precedes infection of the bronchi; however, acute bronchitis may accompany specific infectious diseases such as measles, whooping cough and influenza. It is generally believed that *M. pneumoniae* and the usual respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, adeno-



viruses, rhinoviruses) can also cause acute bronchitis. The disease is prevalent in the winter months.

Symptoms of bronchitis start with malaise, headache, coryza and sore throat; however, cough soon develops. At first coughing is non-productive, but later it yields mucopurulent sputum. Some substernal pain and low-grade fever may be present. Although rhonchi and coarse moist rales may be heard bilaterally, there is usually no abnormality to percussion or auscultation.

Supportive treatment includes bed rest, high humidity, analgesics and antipyretics to relieve malaise and fever and cough syrup. If improvement does not occur by the end of the 1st week, a secondary infection is probable and the use of antibiotics should be considered.

**ACUTE BRONCHIOLITIS.**—Acute bronchiolitis (Figs. 4 and 5), seen mainly in the first 18 months of life, is an acute viral respiratory infection characterized by obstruction of the terminal branches of the bronchial tree, edema, exudate and muscular constriction.

The onset of bronchiolitis is usually insidious, disease begins as an upper respiratory infection with coryza, cough, low-grade fever, irritability and anorexia. Within several days the infant is having rapid, labored respirations, retraction of the intercostal and subcostal spaces, cyanosis and prostration. The cough becomes frequent and exhaustive. Agitation and irritability progress as bronchiolar obstruction increases; prostration and death from anoxia may occur. Physical findings are variable but are usually those of hyperaerated lungs with hyperresonance, evidence of a depressed diaphragm and prolonged expiration with wheezes.

The term “asthmatic bronchitis,” popular in the past, is probably

FIG. 4.—Apprehensive boy, aged 2 months, admitted with minimal fever, cough and rapid labored breathing with retraction of the intercostal and subcostal spaces and the clinical diagnosis of bronchiolitis.





FIG. 5.—Girl, aged 6 weeks, with the clinical diagnosis of bronchiolitis. Roentgenologic examination shows increased vascular markings, hyperaeration and flattening of the diaphragm.

a synonym for this disease, since both diseases are described as having expiratory wheezes, grunting, tachypnea, air trapping and sub-sternal retractions.

The respiratory syncytial virus appears to be the most important single agent causing bronchiolitis; however, para-influenza virus type 3, adenoviruses, rhinoviruses and influenza viruses have also been incriminated.

The treatment of acute bronchiolitis consists of supportive measures to include relief of bronchiolar obstruction, correction of anoxia and anoxemia, awareness of potential cardiac complications and treatment of secondarily acquired bacterial infections. An atmosphere of high humidity with oxygen moistens the exudates and treats the anoxemia. At times epinephrine or aminophylline suppositories relieve bronchiolar spasm, but their benefit is variable. Digitalis may be necessary if heart failure develops, which occurs with enlargement of the liver, gallop rhythm, change in the quality of heart sounds, tachycardia and pulmonary edema. Hydrocortisone therapy has been used in severe bronchiolitis with variable results; the routine prophylactic or therapeutic use of antimicrobial agents is contraindicated.

**DIPHThERIA.**—Diphtheria is a preventable acute infectious disease. Although the disease is worldwide in distribution and prevalent in many developing countries, it should not be neglected in the devel-

oped areas of the world since it is frequently found in inadequately immunized poor people who reside in urban slums. In the United States 152 cases were reported to the Center for Disease Control in Atlanta, Georgia during 1972.

The disease develops after a short incubation period, usually 2-4 days, and may be characterized as nasal, tonsillar, pharyngeal, laryngeal, laryngotracheal or nonrespiratory (skin, conjunctiva or genital area) disease.

The onset of nasal diphtheria is indistinguishable from that of the common cold. It is characterized by nasal discharge and a lack of constitutional symptoms. The nasal discharge, first serous, becomes serosanguinous and then mucopurulent and causes excoriations of the anterior nares and upper lip.

Tonsillar and pharyngeal diphtheria usually begin insidiously with malaise, anorexia, sore throat and low-grade fever. Within a day, smooth, gray-white exudate or membrane appears in the tonsillar area and progresses to involve the uvular, soft palate and pharyngeal wall. Cervical adenitis and periadenitis usually occur and may produce a "bull-neck" appearance.

Laryngeal diphtheria most often develops as an extension of pharyngeal disease, the clinical picture resembles infectious croup. Fever, hoarseness and barking cough are present, with increased obstruction of the airway manifested by inspiratory stridor and supra-sternal, supraclavicular and subcostal retractions. In severe cases, there is increasing obstruction and progressive anoxemia resulting in progressive cyanosis, prostration, coma and ultimately death. A piece of membrane may suddenly detach, obstruct the airway and be associated with sudden, acute fatality.

Myocarditis is a frequent complication of severe diphtheria; however, it sometimes follows milder forms and usually appears during the 2d week of disease.

In general, neuritis is a complication of severe diphtheria and occurs after a latent period. It causes bilateral motor involvement. Clearing is complete if the patient survives. Manifestations include paralysis of the soft palate, ocular palsy, paralysis of the diaphragm with neuritis of the phrenic nerve which necessitates artificial respiratory aid, and paralysis of the limbs.

Diphtheria antitoxin must be given promptly and in adequate doses. Any delay increases the possibility that myocarditis, neuritis or death may occur. Diphtheria toxin may be circulating (unbound), loosely bound or firmly bound to the tissues. Antitoxin will neutralize circulating toxin and may affect loosely bound toxin, but will not affect toxin firmly bound to the tissues. If there is no evidence of sensitivity, antitoxin should be given intravenously so that a high concentration will be immediately available for neutralization of toxin. Antimicrobial therapy is not a substitute for antitoxin therapy but should be given as a supplement to it. Supportive treatment includes

bed rest, maintenance of hydration, an acceptable high-caloric diet and aspirin or codeine for pain. A tracheostomy may be indicated for the relief of obstruction of laryngeal diphtheria. The use of digitalis in patients who acquire myocarditis is controversial; however, it should not be withheld if there is evidence of cardiac decompensation.

A patient is infective until diphtheria bacilli can no longer be cultured from the site of the infection; the duration of this infective period is variable.

Intimate contacts should be isolated and tested with cultures of the nose and throat and Schick tests. If culture and the result of the Schick test are both negative, no action need be taken. Intimate contacts with positive cultures and negative Schick test results should be treated as diphtheria carriers (with antibiotics), and a contact with no symptoms but a positive culture and a positive Schick test result should be treated with diphtheria antitoxin and antibiotics. An intimate contact with a positive Schick test result and a negative culture should be actively immunized with toxoid.

Since 1922 there has been a dramatic decline in the incidence of diphtheria, attributed primarily to mass immunization programs and routine immunizations of infants and children.

## UPPER-LOWER RESPIRATORY INFECTIONS

**INFLUENZA.**—“. . . it began with a roughness of the jaws, small cough, then a strong fever, with a pain of the head, back and legs; some felt as though they were over the breast and had a weight at the stomach; all which continued to the third day at the farthest; there the fever went off with a sweat or bleeding at the nose. In some few, it turned to pleurisy, or fatal peri-pneumony . . .”

This was Short's description of the disease seen in the influenza epidemic of 1557, and it remains difficult to improve on this description today. Influenza remains the only infectious disease capable of assuming pandemic proportions and is considered the most destructive and devastating of all epidemic illnesses. It was responsible for 20,000,000 deaths in the 1918-19 influenza pandemic.

Influenza is a highly contagious disease of the respiratory tract caused by a specific virus and occurring as a sporadic, epidemic or pandemic infection. Sporadic, or endemic, influenza occurs as localized epidemics and is a mild disease, closely resembling the common cold; it subsides in 2 or 3 days with practically no mortality. Epidemic influenza may become pandemic and sweep over a number of countries at a pace more rapid than is explained by person-to-person contact.

An outbreak of influenza depends on the vulnerability of the population and the virulence of the influenza agent. The incubation period is approximately 48 hours. Influenza is spread by droplet in-

fection from one person to another and probably also through the inhalation of contaminated dust, since the virulence of the virus remains unchanged after drying for several days. Persons incubating the disease, those suffering from subclinical infections, those with obvious cases and those convalescing from disease are all sources of infection and probably account for the sudden outbreak of an epidemic.

At the beginning of an epidemic, influenza usually appears as a mild disease attacking people sporadically with negligible mortality. Suddenly it spreads across the nation, affecting a significant number of the population within a short period; when it appears to be subsiding, the epidemic returns with increased virulence and increased mortality for a second and sometimes a third time.

Influenza A epidemics tend to have a cyclic occurrence every 2–4 years, and influenza B epidemics usually occur 4–6 years apart. Type C influenza viruses rarely give rise to epidemics, they usually cause inapparent infections or small outbreaks in children. All pandemics of influenza have been caused by type A viruses. Epidemics of influenza usually occur in the cold months from late autumn to early spring. Within a community the peak of a given epidemic is reached about 2 weeks after onset, and often the epidemic is over in a month. The over-all case fatality rate in epidemics since the 1918–19 pandemic has been low and is probably about 1%. At highest risk are the very young, the very old, the pregnant and persons with underlying cardiopulmonary, metabolic and renal diseases.

Influenza starts with a severe persistent headache, soon followed by pain at the back of the eyes. Within a few hours pain starts in the neck, limbs and back. The temperature rises with chills to 104 F and is usually higher in the evening than in the morning. There is drowsiness, anorexia and cough and the 2d day the patient has infected conjunctiva, a dry tongue and a red and inflamed pharynx. By the 3d or 4th day the temperature is usually normal.

During an epidemic, bronchial or pneumonic involvement is expressed by retrosternal soreness and pain, cough associated with a mucopurulent or bloody sputum, rhonchi and rales and profuse sweating. On the 3d or 4th day there might be an increase in chest pain, cough and respiratory distress, with the appearance of cyanosis and patchy pneumonia seen at the lung bases on x-ray. With more severe infection there is rapid development of heart failure or acute pulmonary edema; death occurs within the first 24 hours or follows pneumonic complications.

Besides these complications, influenza subsequently may be associated with recurrent attacks of colds. Since the influenza virus exerts a profoundly destructive effect on the epithelial lining of the upper part of the whole respiratory tract, the patient becomes excessively susceptible to recurrent attacks of colds and bronchitis.

Influenza vaccines are available for prophylaxis; however, their

use is limited as antigenic difference between the vaccine given and the virus causing the specific epidemic may result in failure of prophylactic vaccination. Even though some protection may occur with an existing vaccine, it is usually incomplete. An optimal vaccine for an influenza epidemic would be one that is developed using the specific strain of influenza virus causing the current epidemic. After vaccination, protective immunity develops within a week, reaches the maximum in about 2 weeks and remains effective for about 1 year.

In general, treatment consists of rest in bed and a diet of semi-solid or liquid food with ample fluid intake to prevent dehydration and to facilitate expectoration. Antibiotics are not indicated for the "flu syndrome" unless secondary bacterial infection occurs. Symptomatic treatment is important to provide comfort and consists primarily of aspirin and codeine to relieve headache, pain and coughing. Inhalation of steam and expectorants may improve the productive cough. Oxygen is indicated for cyanosis and pneumonia.

**PERTUSSIS.**—Pertussis (whooping cough) is an acute infectious disease of the tracheobronchial tree that is manifested by paroxysms of coughing that typically terminate in a whoop and vomiting. The etiologic agent is usually considered to be *B. pertussis*; however, *B. parapertussis* and adenoviruses may also cause a disease indistinguishable from pertussis. Man is the only known host for *B. pertussis*, which usually causes disease in late winter and early spring. Infection appears to be primarily spread by close contact since the organism is capable of surviving for only a short period outside the host. The disease has worldwide distribution and remains endemic in most countries. Clinical, unrecognized or atypical cases and those in the prodromal stages appear to be primarily responsible for the spread of this disease. Unlike most other communicable diseases, females acquire this disease more frequently than do males.

Although pertussis is generally regarded as a disease of children, during recent years there have been reports of clinical disease among older age groups. The incubation period is about 7 days, and if the child is asymptomatic 2 weeks after exposure he most likely has escaped infection.

The clinical course of pertussis may be divided into three stages. The catarrhal stage lasts about 2 weeks and begins with the symptoms of an upper respiratory infection. At times the only manifestation is a hacking cough that gradually becomes more severe, is especially troublesome at night and begins to occur in paroxysms.

The paroxysmal stage lasts 4–6 weeks, as a rule, and the cough becomes frankly paroxysmal. A series of short, rapid coughs, given on one expiration, is followed by a sudden prolonged inspiration associated with a characteristic high-pitched whoop. The typical whoop is usually not heard in infants under age 6 months. During the attack, the child's face becomes red or cyanotic, with bulging eyes, a protruding tongue and an expression of anxiety. A number of parox-

ysms may be grouped together until the last one dislodges a mucus plug. Vomiting frequently follows such an attack and the child then appears listless and dazed. The number of paroxysmal attacks tends to diminish when the child's attention is diverted. Between attacks the patient is usually comfortable.

The convalescent stage is distinguished by an end to the whooping and vomiting and a decrease in the severity of the paroxysms. The cough gradually ceases in 2 or 3 weeks. With subsequent respiratory infections, however, some children will have recurrent paroxysmal coughing attacks, including whooping and vomiting.

The diagnosis of classic whooping cough is often made on clinical grounds during the paroxysmal stage of disease. Leukocytosis with a predominant lymphocytosis is often observed; however, *B. pertussis* is rarely recovered on culture after the 3d or 4th week of illness. As a rule, one attack of whooping cough is followed by lasting immunity.

Complications of this disease include otitis media and bronchopneumonia with subsequent atelectasis and emphysema; central nervous system complications include convulsions secondary to brain damage related to asphyxia from severe paroxysms, massive subarachnoid bleeding and diffuse encephalopathy. Other complications include hemorrhages that are mechanical in origin, resulting from increased venous pressure, and congestion associated with paroxysms; epistaxis and subconjunctival hemorrhages are common. An ulcer of the phrenum under the tongue often may be observed in infants.

The development and use of a potent pertussis vaccine has been associated with a marked decrease in the incidence of whooping cough over the past 3 decades. Because of the high susceptibility of infants, immunization should be initiated at age 6–12 weeks. Pertussis immunization is not recommended for older children or adults because of an apparent increase in untoward reactions.

The problem of preventing disease in exposed susceptible persons has not been resolved. Prophylactic administration of hyperimmune gamma globulin may abort or modify the disease in these persons.

As far as treatment is concerned, evidence suggests that pertussis immune globulin *may* exert a beneficial effect on infants with severe whooping cough. Because of the high mortality among young patients, pertussis immune globulin is recommended for all infants and children under age 2 years who have active disease or who have had intimate contact with a patient with known disease; patients at any age with severe disease deserve to receive the hyperimmune globulin.

Although several antibacterial agents (sulfadiazine, ampicillin, chloramphenicol, erythromycin) have been shown to affect *B. pertussis* *in vitro*, none has effectively modified the severity or shortened the course of the disease.

General treatment includes rest in bed, proper nutrition with extra fluids, the treatment of convulsions with sedatives and oxygen and

the treatment of complications such as pneumonia with appropriate antimicrobial agents.

## LOWER RESPIRATORY INFECTIONS

**ACUTE PNEUMONITIS OR BRONCHOPNEUMONIA.**—The term “bronchopneumonia” includes a variety of reactions of the lung to various agents, infectious and noninfectious, and essentially pertains to an inflammatory disease of the lungs with alveoli involvement.

In 1969, estimates for the United States indicated there were over 2,000,000 cases of pneumonia resulting in almost 35,000,000 days of restricted activity of which almost 22,000,000 were days of bed disability. Of the ten leading causes of death, pneumonia (with influenza) ranks fifth and is first among infectious diseases.

The clinical manifestations vary greatly and depend on the causative agent, the age of the patient, his systemic response to the infection and the degree of bronchial obstruction. Treatment depends on the etiologic agent, and it becomes important to classify pneumonitis on the basis of etiologic agent rather than by location, extent of involvement or radiologic findings. In the antibiotic era bacterial causes of pneumonia have become increasingly better controlled; whether the pneumonia is primary or secondary to a chronic immunosuppressive, noninfectious disease now becomes more important and relevant.

*Bacterial pneumonia.*—*Streptococcus pneumoniae* is associated with a classic picture of bacterial pneumonia and still accounts for about 90% of the cases of this disease (Fig. 6). It is classically a disease of the adult male which is manifested by a shaking chill and a sustained fever up to 106 F. Coughs producing mucopurulent sputum, pleurisy and signs of pulmonary consolidation are also present. Frequently the patient remembers the exact time of onset of the illness because of its abruptness and initial stress. The onset in a child is sudden and may present with vomiting or convulsions. An older child may complain of a headache, abdominal pain or chest pain, and physical examination reveals a temperature elevated up to 104 F, a rapid pulse, rapid shallow respirations and a hot, dry skin. The disease can mimic meningitis in infants with a high fever, convulsions, restlessness, stupor, stiff neck and bulging anterior fontanel; a lumbar puncture is often required to differentiate meningismus from meningitis.

By the 2d day of illness, cough, dyspnea, suppression of breath sounds and rales over the involved area of the lungs enables the physician to correctly diagnose pneumonia. A pleural friction rub and later dullness to percussion and bronchial breathing by auscultation indicate the area of consolidation; the site may be confirmed roentgenologically. The patient begins to improve about 24 hours after appropriate antimicrobial therapy is initiated. Pleurisy is experienced as an excruciating, sharp pain that occurs with every breath. The



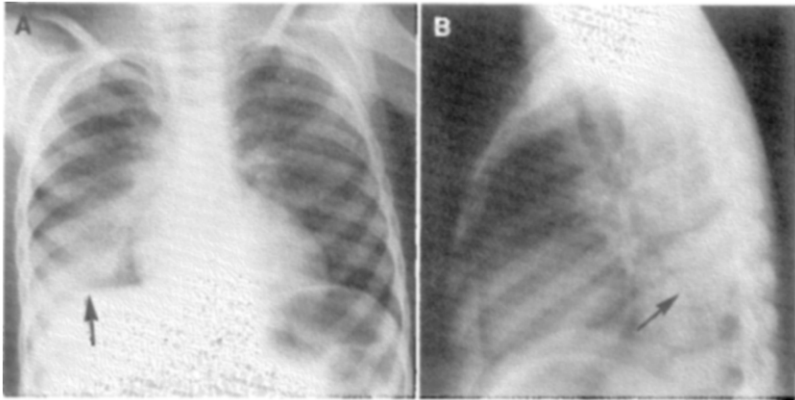


FIG. 6.—Boy, aged 4 years, with fever, minimal cough and severe abdominal pain with guarding and rebound tenderness. Anteroposterior (A) and lateral (B) roentgenologic examination of the chest reveals right lower lobe infiltrates and segmental pneumonia.

chest will lag both in timing and extent of excursion. The patient may labor to breathe using accessory muscles. Resultant hypoxemia may be manifest as cyanosis of the lips or nail beds. Bloody, purulent sputum is produced in streptococcic, staphylococcic and klebsiella pneumonias as well as in pneumococcic pneumonias.

A leukocytosis in the range of 15,000–30,000 cu mm with a marked shift to the left is usual unless the pneumonia becomes overwhelming, and then the total number of leukocytes decreases and immature leukocytes are seen. The roentgenographic changes occur rapidly. Films made early in the course of disease in adults show infiltrates in the region of the hilum with later centrifugal spread, whereas in children the reverse is frequently the case.

Complications such as empyema or lung abscess, pericarditis or endocarditis, bronchiectasis or pulmonary fibrosis, meningitis, arthritis and peritonitis are seen less frequently in this time of antibiotic therapy but may still be expected in up to 20% of cases. Otitis media is common but is treated when the pneumonia is treated. Drug fever may occur with any antibiotic between the 1st and 2d week of therapy.

Hemolytic streptococcic pneumonia may be primary or secondary to other respiratory infections (influenza, measles) or chronic lung disease (asthma). *Haemophilus influenzae* pneumonia, though rare in children, is a primary infection in them. It may be primary in adults; however, it most frequently occurs as a secondary infection in patients with some chronic lung disease. *Klebsiella pneumoniae* causes pneumonia characterized by significant necrosis of the lung, abscess formation and atelectasis; it is usually secondary to another condition such as alcoholism, old age, diabetes mellitus, congestive

heart failure or chronic obstructive pulmonary disease. Staphylococcal pneumonia in infants is acute, fulminant and life-threatening, with cough, cyanosis, tachypnea, fever and pneumatoceles (Fig. 7); in young adults the disease resembles lobar pneumonia and usually follows influenza. The incidence of staphylococcal pneumonia is increasing in children and adults.

The incidence of pneumonia caused by *E. coli*, *Pseudomonas aeruginosa*, enterobacter, bacteroides and proteus species is also increasing. Patients are often older men suffering from conditions such as alcoholism or certain chronic diseases. Patients who are comatose and who are prone to aspirate gastric material will frequently acquire bacterial pneumonia due to gram-negative organisms, as will patients being treated with immunosuppressive drugs, corticosteroids or radiation therapy and patients who have received organ transplants. *Neisseria meningitidis*, nonsporulating anaerobes, *Mycobacterium tuberculosis*, *Francisella tularensis*, *Pseudomonas pseudomallei* and *Yersinia pestis* have all been associated with bacterial pneumonia.

Pneumococcal and streptococcal pneumonia can be treated adequately by any one of a variety of antimicrobial agents including penicillin—the preferred drug—ampicillin, tetracycline, chloramphenicol, erythromycin, sulfonamides and cephalosporins. Whenever possible, the patient should be treated in the hospital because of the advantages of adequate diagnostic facilities. Treatment, in general, consists of a palatable diet, fluids and bed rest, with frequent determinations of vital signs to insure rapid recognition and prompt treatment

FIG. 7.—Girl, aged 2, with fever and in severe respiratory distress. Roentgenologic examination reveals consolidation, pleural effusion and pneumatoceles. Staphylococcal organisms were cultured from pleural fluid.



of any complication. Oxygen should be given when there is evidence of hypoxia. Chest pain and cough will both respond to medications. Occasionally codeine is indicated when the cough is so severe it is associated with lack of sleep. Endotracheal intubation may occasionally be necessary to enable removal of sputum by catheter suction if the patient cannot expectorate. The patient should have complete mental and physical rest, and during convalescence attention should be directed toward comfort and nutritional and emotional needs.

Although a polyvalent vaccine has been proposed for use in patients at the highest risk of death from pneumococcic pneumonia, such a vaccine is not readily available, nor is a study that would indicate its effectiveness.

Most persons with active tuberculosis have no remarkable symptoms until the lesions are quite extensive. Pulmonary tuberculosis may cause little cough and sputum when the lesions are small, but patients with advanced cavitory disease usually have a chronic cough with productive mucopurulent sputum and hemoptysis presenting as bright red streaks of blood intermixed with sputum. Shortness of breath follows extensive spread of infection throughout the lungs or pleural effusions.

The lesions of pulmonary tuberculosis, as seen on roentgenologic examination, may be found early in the apical or posterior segments of the upper lobes; later they may occur as a confluent infiltrate or as a cavity. Also, lesions may occur as multiple discrete nodules scattered in the lung parenchyma adjacent to the confluent or cavitory lesion or they may be in another lobe or in the opposite lung. The specific diagnosis requires the isolation of *Mycobacterium tuberculosis* from sputum, gastric washings, urine or tissue. It is extremely important to make every effort to isolate the tuberculosis organism in order to obtain antibiotic sensitivities. Many strains of *M. tuberculosis* are not sensitive to the usual antituberculous drugs. Chemotherapeutic agents used in this disease are listed in Table 9.

Atypical mycobacteria most frequently causing respiratory infections include Runyon group I mycobacteria, the photochromogens, and Runyon group III mycobacteria, the nonphotochromogens. The diseases caused by *Mycobacterium kansasii* (Runyon group I) and *Mycobacterium intracellulare* (Runyon group III) are clinically and radiologically indistinguishable from classic tuberculosis; however, disease may be more indolent and less often associated with pleural effusion or bronchogenic dissemination. A few instances of chronic pulmonary disease caused by scotochromogenic mycobacteria (Runyon group II) have been reported in adults. Therapy would be similar to that used for *M. tuberculosis* in Runyon group I infections; however, the response is not as good and higher concentrations of drugs are needed. Chemotherapeutic agents are not, as a rule, useful in other atypical mycobacteria infections.

TABLE 9.—ANTITUBERCULOUS DRUGS\*

DRUG	ADMINISTRATION	MG PER KG BODY WEIGHT PER DAY	MAJOR TOXIC MANIFESTATIONS	RELATIVE FREQUENCY OF TOXICITY
Isoniazid	Oral	Initial Treatment 5-10	Neuritis, hepatitis	Uncommon
Streptomycin	Intramuscular	15	Eighth nerve, renal	Common
Ethambutol	Oral	15 (25, retreatment)	Optic neuritis	Uncommon
Para-aminosalicylic Acid	Oral	200	Gastrointestinal intolerance, hypersensitivity	Common
Rifampin	Oral	10	Hepatic	Uncommon
Pyrazinamide	Oral	Retreatment 20-40	Hepatitis	Common
Ethionamide	Oral	7-15	Gastrointestinal intolerance, hepatitis	Common
Cycloserine	Oral	10-15	Psychosis, seizures	Common
Viomycin	Intramuscular	15	Eighth nerve, renal	Common
Kanamycin	Intramuscular	15	Eighth nerve, renal	Common
Capreomycin	Intramuscular	15	Eighth nerve, renal	Occasional

\*From Harris, H. W., and McClement, J. H.: Tuberculosis, in Hoerprich, P. D. (ed.): *Infectious Diseases* (New York: Harper & Row, Publishers, Inc., 1972 [p. 373]).

*Primary atypical or virus pneumonia.*—There are multiple etiologies for primary atypical or virus pneumonia.

A. Viral Etiology.—Influenza viruses, adenoviruses, rubeola, varicella and human cytomegaloviruses have been associated with primary pneumonia in children and adults.

The morbidity and mortality from viral pneumonias vary with the age and physical condition of the host as well as the particular agent involved. Specific etiologic diagnosis is difficult unless viral laboratory studies are available, although the presence of a primary disease such as measles or chickenpox in the presence of pneumonitis may support a specific diagnosis.

Influenza viruses usually cause a tracheobronchitis; however, they may be associated with pneumonia. Primary influenza virus pneumonia usually affects elderly persons who have an underlying chronic, noninfectious process. Within 1 or 2 days, a cough productive of bloody sputum, cyanosis, respiratory distress, high fever and substernal pain develop. The course may progress to death within a few days. Diffuse bilateral bronchopneumonia is found on chest x-rays.

Fatal pneumonias in infants have been associated with adenoviruses types 1, 2, 3, 7 and 7a. Intranuclear inclusions are seen in infected cells and adenoviruses may be recovered from the lung tissue. Atypical pneumonia caused by types 2, 4 and 7 adenoviruses are common in military recruits, but rare in civilian populations. An adenovirus vaccine has been beneficial in preventing disease in military recruits.

The earlier in life the initial exposure to respiratory syncytial virus, the more severe the resulting infection, which varies from a mild upper respiratory infection to bronchopneumonia. Most patients recover completely in 1–3 weeks. Reinfection occurring in older children and adults expresses itself as a mild upper respiratory infection.

Primary measles (rubeola) pneumonia is distinguished by the presence of giant cells possessing intranuclear and intracytoplasmic inclusion bodies. Bacterial pneumonia is one of the serious complications of measles. Children with immunodeficient disorders or with malignant diseases should not receive live attenuated measles vaccine.

Within a week after the onset of chickenpox rash, pneumonia may develop with cough, dyspnea, tachypnea, chest pain and hemoptysis. The vast majority of primary varicella pneumonias occurs in persons over age 19 years; however, the disease does occur in childhood. Chest x-rays generally reveal a pneumonia that is more extensive than would be predicted by physical findings; the bilateral peribronchial infiltrates radiating from the hilum to the periphery of the lung have a characteristic appearance.

Morbidity is significantly increased when pneumonia complicates varicella, with mortality rate approaching 30% instead of the usual rate of less than 1%. Patients with either congenital or acquired immunodeficiencies should receive zoster hyperimmune gamma glob-

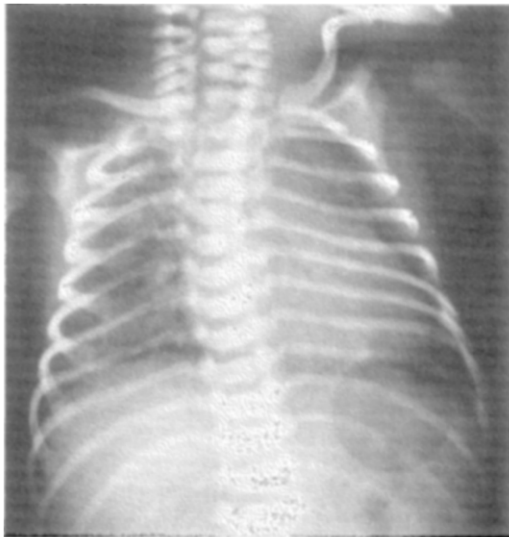
ulin, acquired from the Center for Disease Control, Atlanta, Georgia, after exposure to varicella. There is some indication that cytosine arabinoside may be useful in overwhelming disease with this agent.

The human cytomegalovirus is recognized now as an important cause of pneumonia in infants (Fig. 8) as well as in immunodeficient persons and patients on immunosuppressive therapy. Clinically, the pneumonia caused by cytomegalovirus is impossible to differentiate from other nonbacterial pneumonias, and the etiology must be suspected in a compromised host. Although no controlled studies are available, some patients with pneumonia caused by cytomegalovirus appear to improve when treated with cytosine arabinoside.

**B. *Mycoplasma Pneumoniae* Etiology.**—The most common single etiologic agent of primary atypical pneumonia is *M. pneumoniae*. This agent has been associated with illnesses ranging from inapparent infections to bronchopneumonia. It would appear that mycoplasmal infection is endemic, worldwide in distribution and attacks man only. These agents most likely multiply in the respiratory tract and can be recovered from nasopharyngeal secretions up to 4 weeks after the initial symptoms.

The onset of mycoplasmal pneumonia is usually insidious. Fever, cough, chills and malaise are seen in most patients. Sore throat, nasal congestion, headache and coryza reportedly occur in about half the patients. The fever usually lasts about 8–10 days and then the

FIG. 8.—Premature male infant, aged 1 week, with hepatosplenomegaly, paraventricular intracerebral calcifications, pneumonitis and human cytomegalovirus isolated from throat swabbings and urine. Roentgenologic examination of the chest shows severe interstitial pneumonia.



temperature gradually falls to normal. The complete blood count is usually normal, although occasionally leukocytosis is seen; agglutinations for streptococcus MG may occur and false positive serologic test results for syphilis may appear. The isolation of *M. pneumoniae* from sputum and throat swabs is supportive evidence for the etiology of the disease. Besides the presence of cold hemagglutinins, a complement fixation titer and indirect immunofluorescent staining test are available to support the diagnosis of this disease.

Tetracycline, erythromycin and lincocin have been used in treating primary atypical pneumonia caused by *M. pneumoniae*; however, a definite association with improvement needs to be confirmed.

C. Rickettsial Etiology.—Q fever is an acute, systemic rickettsial disease. The onset is abrupt, with severe headache, chills, fever, myalgia, malaise and pneumonia occurring after a 3-week incubation period. Q fever, first recognized in Australia, is known to occur worldwide and was first recognized in the United States in Montana and California. Although there is no rash, pneumonitis occurs in about half the cases. Hepatosplenomegaly is present but laboratory findings are nondiagnostic. The clinical course is self-limited, lasting up to 3 weeks and having a low mortality.

The definitive diagnosis of Q fever depends on the isolation of *C. burnetii* from the blood, urine or sputum by the careful intraperitoneal inoculation of clinical specimens into guinea pigs. This disease is most contagious and extreme care must accompany the handling of specimens in the laboratory. Complement fixation or agglutination tests are also useful in making a diagnosis.

*Coxiella burnetii* is susceptible to chloramphenicol and the tetracyclines in vitro, but in vivo response is not as impressive. Vaccines that produce protective antibody are available; however, because of a high incidence of local reactions from the vaccine, it is used only in persons at high risk.

D. Chlamydia Species Etiology.—Ornithosis (psittacosis) is an acute disease characterized by fever, malaise, myalgia and pneumonitis occurring when the agent, a chlamydia species, is transmitted to human beings from psittacine birds or other avian genera. Headache, photophobia, sore throat and anorexia with nausea and vomiting also occur. Poultry workers, pet shop workers and pigeon handlers are at high risk.

The ornithosis agent causes natural infections in certain avian species. Although the avian disease may be fatal, infected birds usually have only mild disease. The agent is found in the blood, tissues and respiratory and cloacal discharges of sick birds.

The incubation period is usually 1–2 weeks. Physical findings include fever and a relative bradycardia. Examination of the lungs reveals fine crepitant rales, but signs of true pulmonary consolidation by percussion and auscultation are usually undetectable.

The definitive diagnosis of ornithosis requires isolation of the agent

or the demonstration of a significant rise in antibody specific for ornithosis.

Tetracycline is the drug of choice for the treatment of ornithosis. Chloramphenicol is less effective. Penicillin G has been used in patients sensitive to the tetracyclines. With the help of chemotherapy, parakeets bred in the United States are free from ornithosis.

In summary, the term "primary atypical pneumonia" was derived about 30 years ago to describe a consolidation that differed both clinically and radiologically from a classic pneumococccic pneumonia and for which no apparent cause could be found. Over the years, it was realized that this type of pneumonia was caused by agents too small to be collected on a bacterial filter, therefore, the etiology was presumed to be viral. Despite the diversity of etiologic agents (viruses, rickettsia, mycoplasma, chlamydia) now known to be associated with primary atypical pneumonia, the clinical picture is more or less the same. The onset of the illness may be insidious, with cough, malaise, low-grade fever and headache. At times the illness begins with abrupt chills, high fever, headache and severe body aches and pains. The cough, present from the start or developing later, is usually never very distressing. In contrast with lobar pneumonia, chest pain and respiratory distress are minimal. Chest x-rays show a confluent, hazy opacity spreading out from the hilus or involving segmental areas of the lung. Radiologic changes may be much more extensive than the clinical picture would suggest. The disease runs a benign course and symptoms usually disappear in about 10 days, although the x-ray changes may persist for several weeks. Complications are rare.

Treatment is symptomatic with antipyretics, analgesics and cough remedies. The place of antibiotics in the treatment of this disease is still not fully established but they should be considered if the etiology is mycoplasmal, rickettsial or chlamydia species.

*Parasitic infections.*—Parasitic infections of the lungs are a frequent occurrence in the tropics. With today's ease and frequency of air transportation to any point in the world, it is possible that persons who have visited endemic zones will subsequently acquire such lung infections when they return to areas where parasitic lung infections are unknown to occur.

A. *Pneumocystis Carinii* Pneumonia.—*Pneumocystis carinii* pneumonia affects the immunosuppressed host and the debilitated infant. The disease has almost always been sporadic, rarely epidemic, and has occurred in all age groups. It is well known to occur in children with primary immune deficiency disorders, in patients receiving immunosuppressive drugs for lymphoreticular malignancies and in patients with organ transplantations.

Overt disease with *P. carinii* most likely represents the activation of a latent infection favored by many factors that diminish the host's resistance. The pneumonia caused by *P. carinii* is most frequently



described as an interstitial plasma cell pneumonia. The signs and symptoms of the pneumonia are often obscured by the underlying disease itself or by an infection with other pathogens. Attempts at making a specific diagnosis by the examination of stained sputum and from tissue obtained by percutaneous lung biopsy have been successful in isolated situations; however, these methods have failed frequently enough to establish open lung biopsy as the procedure of choice as a diagnostic tool. A complement fixation test using an antigen prepared from infected lung tissue has been used for diagnostic purposes but not with consistent success in the United States.

As far as therapy is concerned, pentamidine isethionate has been used most extensively and can be obtained from the Center for Disease Control in Atlanta, Georgia. Spontaneous recoveries do occur; therefore, the true effectiveness of specific chemotherapy is difficult to determine. The combination of pyrimethamine and sulfadiazine was highly effective in experimental *P. carinii* infections, but its value in treating human disease is still being assessed.

B. Toxoplasmosis.—The occurrence of a congenital form of toxoplasmosis has been known for many years and acquired toxoplasmosis is not a rare disease. The pulmonary lesions in this disease are characterized by an interstitial inflammation involving the perivascular and peribronchial tissues. Lymphocytes, plasma cells and large mononuclear cells are found in pathologic specimens of the alveoli and are associated with variable degrees of bronchopneumonia. The chest x-rays reveal dense hilar shadows and accentuation of the lung markings bilaterally with irregular areas of density in the lower lobes.

A combined treatment course of sulfadiazine and pyrimethamine has produced encouraging results in a limited number of human infections, but the drugs affect only the free-floating organisms, not those encysted.

C. Paragonimiasis.—The type of pulmonary manifestations due to *P. westermani* depends on the severity of infection. Patients have fever, prostration, minimal cough and occasionally hemoptysis. At times the dyspnea and prostration are more severe, with pleuritic pain. Chest x-rays reveal lesions or patchy infiltrates in the lower lung fields. Diagnosis can be made by finding the characteristic ova on examination of the sputum or the stool.

*Paragonimus westermani* infection frequently produces chronic disease and is occasionally fatal in patients experiencing very heavy infestation. Some patients appear to benefit from either chloroquine or emetine, although there is no consistently effective therapy.

D. Echinococcosis (Hydatid Disease).—Initial symptoms of hydatid disease of the lungs consist of cough, hemoptysis and pleuritic pain. Sputum is sparse and there is little fever. Physical examination is unrewarding in comparison to roentgenologic exam, which shows one or more discrete round lesions which are sharply defined, have

little surrounding inflammatory response and are sometimes calcified. If the cyst extends locally, it may compress the esophagus and produce profound dysphagia or a superior vena caval syndrome. Once the cyst has ruptured into the bronchus, pleural space or lungs, secondary bacterial infection is common and may be followed by chronic abscesses. Simple pulmonary hydatids have no bronchial communication; the disease is considered complicated if bronchial or pleural communications are present. The outstanding feature of the disease is its latency, the presence of hydatids often being recognized by chance. Rupture of a cyst with escape of a large amount of fluid may drown the patient, and fluid escaping into the tissues may give rise to hypersensitivity manifestations associated with pruritis, urticaria, cyanosis, dyspnea and, occasionally, vascular collapse.

The most important laboratory test is the finding of hydatid elements in the sputum. A skin test is available but may be falsely negative. The treatment of choice is segmental resection unless the cyst is unusually large or multiple and considerable lung tissue is involved.

E. Amebiasis.—*Entamoeba histolytica* may infect the lungs. In about half the patients, abnormalities of the chest x-ray consist primarily of an elevation of the right leaf of the diaphragm because of hepatomegaly. The lateral projection may show a bulge of the anterior half of the diaphragm and the right lower lung field may show secondary changes simulating pneumonia or fluid at the costophrenic angle. Pain on respiration, an early symptom caused by hepatic abscess, may be referred to the shoulder; pulmonary involvement is associated with hemoptysis, cough, dyspnea and mucopurulent sputum.

A suspect diagnosis may be supported by identifying *E. histolytica* ova in sputum or stool specimens or by a positive serology test. The treatment is directed to the trophozoites, the vulnerable form of the ameba. In the past, emetine and chloroquine have been used; however, metronidazole is currently the drug of choice. Paromomycin, an investigational drug, and dehydroemetine are alternate drugs found useful in the treatment of *E. histolytica* infections.

F. Schistosomiasis.—Up to one-half the patients with severe schistosomiasis manifest some degree of pulmonary involvement, and a small percentage have cor pulmonale. Pulmonary involvement usually is chronic and accompanied by extrapulmonary schistosomal involvement such as hepatosplenomegaly. Dyspnea and nonproductive cough are the most common symptoms. Chest signs are usually absent clinically, although patients occasionally have fine inspiratory rales or inspiratory and expiratory rhonchi. Schistosomal lung disease may occur as an acute process related to an intense inflammatory response of the lung to ova invasion and manifested by severe respiratory distress, productive cough, hemoptysis and cyanosis. Roentgenologically, the lung fields may be normal or show diffuse infiltrates. Results of pulmonary function studies vary. Some patients demonstrate an obstructive pattern with diminished maximum breath-

ing capacity in the presence of a relatively good vital capacity. If ova are found in the sputum of a patient with acute pulmonary disease, treatment should be initiated with potassium antimony tartrate intravenously or stibophen, a trivalent antimony compound, intramuscularly. These drugs may induce myocardial or hepatic damage, and drug-induced Loeffler's syndrome may occur during therapy. Nirdazole and lucanthone are experimental drugs used for *Schistosoma haematobium* and *Schistosoma mansoni* infestations.

G. Visceral Larva Migrans (Löffler's Syndrome).—In 1932, Löffler described a mild disease that lasted about a week and was characterized by pulmonary infiltration with patchy, fleeting and migrating abnormalities on chest x-ray and remarkable peripheral eosinophilia (82%). Although a moderate cough was present, most of the patients did not have fever or produce sputum. It is not certain whether the symptoms and the infiltration on chest x-rays are the result of direct invasion of toxocara larvae or a hypersensitivity reaction. Hyperglobulinemia occurs in about 60% of the patients with this syndrome and isohemagglutinin titers are frequently elevated. A specific hemagglutination titer is available from the Center for Disease Control in Atlanta, Georgia; fluorescent antibody tests may also be helpful in supporting this diagnosis. Since the original description by Löffler, it has become evident that the disease may persist for a longer period and the etiology may be variable, although at present the larval form of *Toxocara canis* or *Toxocara cati* is considered the most frequent etiology. Treatment with thiabendazole and diethylcarbamazine has been tried, but not with consistent success.

*Fungal infections.*—Most fungus infections are sporadic diseases with worldwide distribution. About forty species are pathogenic to man and are assuming greater importance as agents causing infections of the respiratory tract.

A. Actinomycosis.—Actinomycosis, caused by *Actinomyces bovis*, is classified clinically as (1) cervicofacial, (2) thoracic and (3) abdominal. Thoracic, or pulmonary, actinomycosis manifests itself as a chronic disease producing symptoms of fever, malaise, cough and purulent sputum, indicating low-grade pneumonitis. Spread to the pleura is frequent, with resulting empyema and sinus formation through the chest wall. The x-ray film shows diffuse, nodular or circular shadows, often with hilar adenopathy. The diagnosis is made by examination of sputum or pus from a discharging sinus that contains "sulfur granules" that may show radiating mycelia. Treatment is with large doses of penicillin for a prolonged period (4 months or longer).

B. Nocardiosis.—Nocardiosis, caused by *Nocardia asteroides*, produces multiple abscesses and at times sinus tracts resembling actinomycosis. There may be a primary granulomatous infection of the lungs resembling tuberculosis or a super-infection when other

pulmonary disease is present. Treatment consisting of large doses of penicillin must be continued for 4 months or longer. Sulfadiazine and streptomycin have also been used successfully.

C. Cryptococcosis (Torulosis).—Cryptococcosis is a generalized granulomatous disease that favors the lungs and meninges. The pulmonary lesion caused by cryptococcus is a massive inflammatory reaction resembling pneumonia on the x-ray film. The infection also produces miliary disease or a solid mass of granulomata resembling a tumor. Cases may be benign or chronic and the diagnosis is usually confirmed by examination of the sputum, exudate or cerebrospinal fluid showing yeastlike cells. Amphotericin B intravenously combined with symptomatic treatment and surgery sometimes helps. Some cases of cryptococcal pulmonary infection have responded to 5-fluorocytosine.

D. Histoplasmosis.—When a previously uninfected person inhales dust containing the spores of *Histoplasma capsulatum*, multiple small infiltrative areas form in the lungs. With a small infecting dose there is no illness, but with a large dose there is an acute illness, usually benign, 2 or 3 weeks after infection. After a few weeks of fever and sometimes months of poor health, complete recovery is the rule. Some heavily infected infants and children with poor general resistance die of generalized histoplasmosis. Other patients, usually middle-aged men, acquire a chronic cavitary lung disease resembling chronic pulmonary tuberculosis, with slow progression of disease toward a fatal outcome. Diagnosis is confirmed by a positive histoplasmin skin test, a complement fixation test and identification of *H. capsulatum* in bronchial secretions. Amphotericin B is the chemotherapeutic agent of choice. The optimal dose, the duration of therapy and the total amount of drug needed for treatment of this disease are all not definitely known. Surgery is sometimes necessary to resect a solitary pulmonary nodule; general supportive care is important.

E. Blastomycosis.—When infection with *Blastomyces dermatitidis* involves the lungs, there is a progressive, suppurative granulomatous disease resulting in death within 5 years. Early symptoms include cough, fever, dyspnea, anemia and progressive prostration. X-rays show mediastinal enlargement with hilar lymphadenopathy and miliary disease. Diagnosis is made by culturing the fungus from the sputum and/or pus and by positive skin tests and complement fixation tests. Amphotericin B is the drug of choice; successful treatment has occurred with oral administration as well as with comparatively low intravenous doses of the drug. 2-Hydroxystilbamidine is administered intravenously, has few toxic reactions and may be considered as therapy for milder forms of blastomycosis. Saramycetin, a polypeptide antibiotic that is administered subcutaneously, has significant activity with few toxic reactions in a number of serious fungal infections. This drug, along with hamycin, which is also effective in blastomycosis, is available only for investigational purposes.

F. *Coccidioidomycosis*.—Primary coccidioidomycosis, caused by *Coccidioides immitis*, when asymptomatic is diagnosed by a positive skin test. It may also occur as an illness of variable severity consisting of fever, malaise, cough, cervical adenopathy and arthralgia. Symptoms last for several weeks and convalescence is prolonged, as in any severe respiratory tract infection. Repeated hemoptysis is common because if cavities occur they persist indefinitely and become reinfected. The disseminated form of the disease is characterized by recurrence of symptoms due to extension of the disease; metastatic abscesses may be found in various organs.

The chest x-ray in the acute stage shows patchy areas of pneumonia with increased markings and enlarged tracheobronchial lymph nodes; subsequent x-rays may show a spherical, solitary granuloma, the so-called coin lesion. The sputum may show the characteristic spherules of *immitis* on smears or the cultures may be positive. Results of the complement fixation test become positive within 3 weeks but may become negative with recovery. The coccidioidin skin test result becomes positive within a week of the onset of fever but may become negative with dissemination, probably due to anergy. Treatment consists of rest in bed, symptomatic treatment and amphotericin B for disseminated disease.

G. *Candidiasis*.—Bronchopulmonary infection due to *C. albicans* occurs frequently enough to be considered in the differential diagnosis of an obscure disease of the lungs and bronchi, especially in patients suffering from chronic diseases or in patients treated with broad-spectrum antibiotics. The infection is acquired by inhalation of the organism from the upper respiratory tract when there is loss of tissue resistance or disturbed normal bacterial flora. An x-ray of the chest shows extensive infiltration of both lungs. Diagnosis is suggested by the presence of budding yeast cells and filaments on examination of bronchial secretion or by culturing the organism. Although nystatin has been useful for minor infections caused by *C. albicans*, serious bronchopulmonary infections are usually best treated with amphotericin B. There is some evidence that the use of 5-fluorocytosine has been associated with successful treatment.

H. *Aspergillosis*.—*Aspergillus niger* is often isolated from sputum of patients suffering from tuberculosis or other chronic pulmonary diseases; it is difficult to establish the pathogenicity of the fungus as it may be a saprophyte or a contaminant. Symptoms of pulmonary aspergillosis include severe cough with purulent expectoration, recurrent fever and weight loss. X-ray of the chest shows dense lesions with cavities that cannot be distinguished from tuberculosis. Diagnosis may be made by sputum examination and culture. Surgical resection has been the usual treatment of the fungus ball due to aspergillosis. Intravenous therapy with amphotericin B is less effective in aspergillosis than in other fungus infections because the course of severe forms of disease is usually so fulminant that there is not enough time

to obtain therapeutic effect from the drug and because aspergillus species are relatively resistant to amphotericin B. Two antifungal agents not presently available in the United States, pimaricin and saramycetin, have been given therapeutic trials in Great Britain and Japan.

I. Mucormycosis.—Although mucormycosis caused by *Mucor absidia* and *M. rhizopus* is primarily a disease of the brain or associated with immunodeficiency diseases or states, occasionally the lungs and other organs are infected. Pulmonary infection is characterized by sudden onset with severe chest pain, pleural friction rub, blood-stained sputum and consolidation on chest x-ray. Treatment consists of autogenous vaccine and potassium iodide orally; amphotericin B has been effective in a number of patients although in vitro testing indicated resistance.

*Necrotizing pneumonia and lung abscess.*—The bacteriology of necrotizing pneumonia and lung abscess is not well documented, but probably more than half of these infections are caused by anaerobic bacteria. Anaerobes most often isolated in patients with this disease include *Bacteroides melaninogenicus*, *Bacteroides fragilis*, *Fusobacterium fusiforme*, *Spherophorus* sp., various anaerobic and microaerophilic cocci and streptococci, and eubacterium species. Because anaerobes are normally present in the mouth and upper respiratory tract, expectorated sputum is not suitable for culture. Transtracheal aspiration and transthoracic lung puncture are appropriate techniques for obtaining specimens, which must immediately be placed under anaerobic conditions. The most common aerobic causes of necrotizing pneumonia are *S. aureus*, *S. pyogenes*, *K. pneumoniae*, *P. aeruginosa* and occasionally *E. coli*.

The disease usually starts with fever, malaise, cough and pleurisy. The cough becomes productive of large amounts of purulent sputum that is foul-smelling, the hallmark of an anaerobic infection. On physical examination there is evidence of pneumonia with or without pleurisy and an x-ray reveals numerous small cavities, usually within a pulmonary segment or lobe. Leukocytosis and anemia are frequently present. The prognosis depends on the type of underlying or predisposing pathologic process and the speed with which appropriate antibiotic therapy is begun. Prolonged therapy, up to 4 months, is necessary to prevent relapse. In addition to antibiotic therapy (Table 10), postural drainage is an important aspect of management of lung abscess. Bronchoscopy may occasionally be helpful to institute good drainage. Tracheostomy and frequent suctioning may be necessary in some patients.

*Empyema.*—Acute empyema, purulent fluid in the pleural cavity, usually occurs secondary to pneumonia or to a lung abscess but may result from seeding during septicemia. Extension from mediastinal lymph nodes or paravertebral abscesses occurs primarily in granulomatous infections. At first there is an exudative phase with thin

TABLE 10.—SUSCEPTIBILITY OF ANAEROBES TO SOME ANTIMICROBICS\*†

ANTIMICROBIC	ANAEROBIC COCCI	GRAM-NEGATIVE BACILLI		GRAM-POSITIVE BACILLI	
		<i>Bacteroides fragillis</i>	Other	<i>Clostridium sp.</i>	Nonsporu- lating
Penicillin G	4+	1+	4+‡	4+	3+ to 4+
Chloramphenicol	3+	4+	3+	3+	2+ to 3+
Tetracycline	2+‡	1+	3+	2+ to 3+	3+
Erythromycin	3+	1+	1+ to 2+	3+	2+ to 3+
Lincomycin	3+	1+	3+‡	3+	?3+
Vancomycin	3+	?1+	?1+	3+	2+ to 3+
Clindamycin§	4+	3+ to 4+	3+‡	3+ to 4+	3+ to 4+
Metronidazole§	3+	4+	4+	3+ to 4+	3+ to 4+

\*From Feingold, S.: Necrotizing Pneumonias and Lung Abscess, in Hoerprich, P. D. (ed.): *Infectious Diseases* (Hagerstown: Harper and Row, Inc., 1972 [p. 349]).

† 4+, drug of choice; 3+, good activity; 2+ moderate activity; 1+, poor or inconsistent activity.

‡ Few strains resistant.

§ Clinical efficacy not established.

fluid and a low cell count. Next, fibrin and polymorphonuclear leukocytes collect in the fluid and the fluid becomes loculated posteriorly and laterally. Finally, fibroblasts produce an inelastic membrane that ultimately may need to be decorticated.

Common clinical manifestations include fever, sweating, chest pain, anemia, leukocytosis and weight loss. The physical findings are those of pleural effusion; a lateral decubitus chest film or fluoroscopy usually demonstrates the collection of fluid. Fluid should always be obtained and examined in regard to volume, color, consistency and odor, specific gravity, total protein, red and white blood cells and differential, gram stain, acid-fast stain, wet mount for fungi, culture for aerobic and anaerobic bacteria, tubercle bacilli and fungi and cytology (cell block). The fluid may vary from cloudy material with fibrin to frank pus. Purulent exudates that are sterile on culture may be related to previous antimicrobial therapy. Other studies, such as blood cultures, should be obtained to rule out distal sites of infection.

Empyema is treated by appropriate antimicrobial agents, provision for adequate drainage and obliteration of dead space. In the early stages of empyema, repeated thoracentesis may provide adequate drainage; however, if the patient remains toxic or fluid reaccumulates rapidly, continuous closed drainage may be necessary. Decortication, or removal of the empyema sac, may be necessary to allow expansion of the lung to obliterate dead space.

## PROBLEMS WITH IMMUNOPROPHYLAXIS

Chanock and Parrot several years ago identified many of the problems interfering with the development of an effective and prac-

tical vaccine for the prevention of respiratory disease. The vast number of respiratory tract pathogens constitutes the major obstacle to a rapid and simple solution of this problem. Secondly, many of the significant viral pathogens do not replicate in tissue cultures that can be used for vaccine production, or the quantity of protective antigen produced is insufficient to stimulate antibody in human beings. Also, a satisfactory antibody response does not always follow inoculation with a concentrated antigen preparation. A number of difficulties exist concerning the safety of vaccines for human use. For example, adventitious agents occur commonly in the two host systems most often used for vaccine production, monkey kidney tissue culture and the embryonated egg. Vaccines that are free of adventitious viruses are not necessarily safe since the vaccine strain itself may possess oncogenic activity. It is known that adenoviruses can induce tumors in hamsters, as well as in other animals, and virus strains with known oncogenic activity in experimental animals should be excluded from vaccines designed for human use.

Effective immunization must occur in early infancy for appropriate RSV, parainfluenza and adenovirus protection; however, the immunologic responsiveness is poor at this age because maternal antibody is still present. A final problem is that moderate levels of antibody may fail to prevent reinfection and associated illnesses.

Over 50% of the serious respiratory illnesses of early life can now be explained by organisms that may be cultivated in the laboratory. This fact, along with an awareness of potential hazards to vaccine safety, should be tantamount to a successful immunoprophylaxis program. Unfortunately, difficulties still exist and vaccines available for acute respiratory diseases are few in number and not optimal in effectiveness.

## THE ANTIBIOTIC CONTROVERSY

To treat or not to treat—that is the perennial question for the clinician who is evaluating an acute respiratory infection. Except for specific diseases, such as diphtheria, the specific pneumonias, such as staphylococcus, and empyema, by definition, all upper respiratory infections, infections causing airway obstruction, upper-lower respiratory infections and lower respiratory infections may be caused by viruses. If the primary infection has a viral etiology, then antibiotic therapy is not indicated. Unfortunately, all of these syndromes also may be caused by bacterial agents, or secondary bacterial infections may follow primary viral infections—and therein lies the problem and the dilemma.

Bacterial cultures should be taken to help make the decision of whether or not to treat, but at times a decision to initiate antibiotics must be made prior to the availability of culture results. Certain



TABLE 11.—COST OF ANTIBIOTICS TO TREAT OTITIS MEDIA\*

PREPARATION AND AMOUNT REQUIRED	COST OF PACKAGED ITEM†	COST OF VOLUME REQUIRED†
Single injection of C-R Bicillin (300,000 units each benzathine-procaine penicillins)	\$ 2.00	\$ 2.00
Three daily injections of procaine penicillin followed by C-R Bicillin	1.00 per injection 2.00	\$ 3.00 2.00
		\$ 5.00
Single injection of C-R Bicillin followed by sulfisoxazole, 500 mg per 5 cc	2.00 2.25/120 cc	\$ 2.00 3.00
		\$ 5.00
Oral penicillin G 200,000 units per 5 cc	1.75/100 cc	\$ 3.50
Phenoxymethylpenicillin 125 mg per 5 cc	3.75/200 cc	3.75
Ampicillin, 250 mg per 5 cc	10.75/200 cc	10.75
Erythromycin, 200 mg per 5 cc	5.50/100 cc	11.00
Clindamycin, 75 mg per 5 cc	5.60/100 cc	11.20
Cephalexin, 125 mg per 5 cc	7.25/100 cc	14.50
Amoxicillin, 125 mg per 5 cc	6.00/80 cc	15.00

\*Modified from Lewis, K. H.: Antimicrobial Therapy in Respiratory Tract Disease, *Pediatr. Clin. North Am* 15:200, 1968.

†Costs based on treatment of a 10-kg child for 10 days. Patient prices at the Childrens Hospital of Los Angeles as of April 1, 1974.

TABLE 12.—ANTIMICROBIAL THERAPY IN ACUTE RESPIRATORY DISEASE

INFECTING ORGANISM	ANTIMICROBIAL THERAPY	
	Preferred	Alternate
Bacteria		
<i>Streptococcus pneumococcus</i>	Penicillin G	Erythromycin, clindamycin
<i>Haemophilus influenzae</i> , type b	Ampicillin	Chloramphenicol
Group A $\beta$ -hemolytic streptococcus	Penicillin G	Erythromycin, clindamycin
<i>Staphylococcus aureus</i> , coagulase +		
Non-penicillinase-producing	Penicillin G	Cephalexin, clindamycin, (IV) cephalothin
Penicillinase-producing	(PO) Dicloxacillin (IV) Methicillin	Cephalexin, clindamycin Clindamycin, gentamycin, cephalothin
Bacteroides (except fragilis)	Penicillin G	Clindamycin, chloramphenicol
<i>Corynebacterium diphtheriae</i>	Penicillin G	Erythromycin

<i>Bordetella pertussis</i>	Ampicillin	Erythromycin
<i>Mycobacterium tuberculosis</i>	Isoniazid combined with Para-aminosalicylic acid, with or without streptomycin	Ethambutol, ethionamide, cycloserine, kanamycin (according to sensitivities)
<i>Pseudomonas aeruginosa</i>	Gentamycin with carbenicillin	Polymixin B, amikacin
<i>Klebsiella pneumoniae</i>	Gentamycin	Cephalothin and/ or kanamycin
<i>Escherichia coli</i>	Gentamycin	Ampicillin and/ or kanamycin
Viruses		
Herpesviruses ( <i>H. simplex</i> , varicella-zoster, CMV)		Cytosine arabino- side, adenine arabinoside (experimental)
Influenza A <sub>2</sub>	Amantadine (prophylaxis)	
Fungi*		
<i>Histoplasma capsulatum</i>	Amphotericin B	
<i>Coccidioides immitis</i>	Amphotericin B	
<i>Actinomyces israeli</i>	Penicillin G	Tetracycline
<i>Nocardia asteroides</i>	Sulfonamides	Cycloserine
<i>Blastomyces dermatitidis</i>	Amphotericin B	2-hydroxystilbamidine
Other agents*		
<i>Mycoplasma pneumoniae</i>	Erythromycin or tetracycline	
Chlamydia species	Tetracycline	Chloramphenicol
<i>Pneumocystis carinii</i>	Pentamidine isethionate	Pyrimethamine and sulfadiazine
<i>Toxoplasma gondii</i>	Pyrimethamine and sulfonamides	
<i>Coxiella burnetii</i>	Tetracycline	Chloramphenicol

\*For treatment of other fungi and other parasites, see text.

factors that affect the decision to start antibiotics prior to receiving information on cultures would include: the suspected kind of infection and the natural history of such an infection if treatment were delayed, how long the patient had been sick prior to being evaluated medically, the age of the patient, evidence of underlying disease, the reliability of the parent and, finally, epidemiologic factors, that is, what diseases are prevalent in the community.

If the history and physical examination determine that the patient has lobar pneumonia, acute epiglottitis or acute otitis media, then treatment must be initiated to prevent death or such severe complications as empyema, bacteremia and mastoiditis. On the other hand, if the patient has an upper respiratory infection or vesicular tonsillopharyngitis, then withholding antibiotic therapy until bacterial cul-

tures are available would be reasonable, since these diseases are almost always due to a virus. Unfortunately, the "gray zone" includes the vast majority of acute respiratory infections and these are the situations that tax the clinician's diagnostic acumen.

As far as treatment of acute respiratory diseases is concerned, the costliest medication prescribed is usually the antibiotic. There is a wide variation in the costs of antibiotics, as illustrated in Table 11. It would seem reasonable to consider this factor in making a decision about the antibiotic to use if therapy for the patient is not compromised.

Finally, a number of factors must be considered in choosing an antibiotic once the decision has been made to initiate therapy: the clinical impression, the identification of the etiologic agent, the nature of the infection, certain host factors such as age, allergy, epidemiologic factors, potential toxicity of drugs and the physician's preference based on previous experience in the same community. Table 12 lists the author's preference for antibiotics to treat the etiologic agents causing the clinical syndromes discussed.

## SUMMARY

In conclusion, the purpose of this dissertation has been to review the data on acute respiratory infections as to etiology, pathogenicity, clinical syndromes and treatment. It would take volumes to adequately discuss respiratory infections in all their complexity, and by the time any manuscript gets into print, it is likely to be outdated because of the rapid advances in the area of virology and antimicrobial agents. This review in no way claims completeness for any one subject, but an attempt has been made to bring into focus and with some sort of organization the vast amount of information in the literature, recent and old, relative to acute respiratory infections.

Perhaps the most encouraging aspects of acute respiratory infections are the mildness and short duration of the vast majority of these diseases, aspects which have been well expressed by A. A. Milne:

Christopher Robin  
Had wheezles  
And sneezles,

. . .

Christopher Robin  
Got up in the morning,  
The sneezles had vanished away.  
And the look in his eye  
Seemed to say to the sky,  
"Now, how to amuse them today?"

(From *Now We Are Six* [New York: E. P. Dutton & Co., Inc., 1950] pp. 12-14).

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## REFERENCES

A recent review of newer respiratory viruses in childhood (Cherry, 1974) listed 432 references. The present author in no way claims to list all the sources of information used in preparing this manuscript, but has selected key references, many of which contain excellent bibliographies, that pertain to all aspects of the discussion.

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