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Clinically Distinguishable Syndromes Caused by Viruses

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INTRODUCTION

THE ROLE of viruses in the etiology of infectious diseases of children was emphasized by physicians taking care of children long before there was actual evidence of the importance of viruses. Indeed, all parents are accustomed to the frequent incrimination of viruses as the cause of illness in their children. It is, and has been for many years, common practice to blame viruses for a wide variety of illnesses characterized by fever alone or by fever and any number of other symptoms such as nausea, vomiting, diarrhea, sore throat, rhinorrhea, cough, skin rashes, myalgia, arthralgia and malaise, to name but a few.

As virologic technics have become less cumbersome, less expensive and more available, it would appear that the physician who has invoked the virus as the cause of numerous illnesses has probably been correct most of the time. On the basis of studies of etiology and epidemiology it would appear that viruses are responsible for perhaps as many as 90% of the etiologically diagnosed infections in children.

We have been fortunate enough to have at our disposal a virology laboratory, which is used for epidemiologic studies and for routine diagnostic procedures. This discussion of clinically recognizable viral syndromes draws heavily on the experience gained from these studies and on the published experiences of others. We hope this information will be helpful to the physician who cares for children but who must function without extensive laboratory support. We hope, in addition, to emphasize that the diagnostic virology laboratory has come of age. Technics are currently available that will give the practicing physician

specific etiologic information rapidly and at a reasonable cost. In the absence of such diagnostic facilities a careful history, physical examination and generally available laboratory studies will enable the physician to recognize a wide variety of clinical syndromes caused by viruses, and in some cases the specific virus can be named with a high degree of accuracy. Unfortunately many viral diseases do not produce clinically recognizable syndromes, and others closely mimic bacterial infections. In these patients viral diagnostic studies are most helpful.

Diagnosis of Viral Diseases

Innumerable viruses are known to cause infections in human beings. These viruses contain either deoxyribonucleic acid (DNA) or ribo-

TABLE 1.—Viruses That Frequently Cause Infections in Children

- DNA Viruses
  - Herpesviruses
    - Herpes simplex
    - Varicella-zoster
    - Cytomegalovirus
    - Epstein-Barr
  - Papovaviruses
    - Human wart
  - Poxviruses
    - Vaccinia
    - Smallpox
    - Molluscum contagiosum
  - Adenoviruses
- RNA Viruses
  - Arboviruses
    - St. Louis encephalitis
    - Western equine encephalitis
    - Eastern equine encephalitis
    - California encephalitis
  - Coronaviruses
  - Picornaviruses
    - Enteroviruses
      - Polioviruses
      - Coxsackie—group A and group B
      - ECHO
    - Rhinoviruses
  - Myxoviruses
    - Orthomyxoviruses
      - Influenza A
      - Influenza B
      - Influenza C
    - Paramyxoviruses
      - Parainfluenza, types 1–4
      - Mumps
      - Measles
      - Respiratory syncytial

nucleic acid (RNA). This permits a convenient basis for classification in two major groups, as shown in Table 1. This classification serves a very useful purpose since closely related viruses share characteristics that may be determinants of the type of disease produced, and it may be that the nucleic acid type will be a determinant in the sensitivity to chemotherapeutic agents.

One approach to the diagnosis of viral infections is to classify the diseases that may be produced by a single virus. Herpes simplex virus, for example, is capable of producing illnesses that may involve one or several organ systems, with a spectrum of severity.

Another approach is to classify the diseases according to the organ system involved and, when this is expanded to include the age of the patient and the season of the year, it is possible to enumerate the viruses most likely to produce the illness. This is the most useful clinical approach to the diagnosis of viral infection. Some viruses, particularly those with a single serotype or those with a small number of serotypes, generally cause infections in younger patients; specific antibody then develops that in many instances renders the patient permanently immune. Measles virus is a good example. There is a single serotype, and the disease is highly contagious so that almost all children have measles. The disease is rare in adults.

We find it convenient to use the organ syndrome approach. First, an anatomic diagnosis such as acute bronchiolitis is made. Second, in the case of bronchiolitis, the patient usually is under the age of 1 year. When all of the criteria for the diagnosis of acute bronchiolitis are met, we may be almost certain that the disease is caused by one of three viruses, respiratory syncytial virus (RSV), adenovirus or parainfluenza virus.

Seasonal factors also are of utmost importance. In central Ohio enteroviruses cause infections almost exclusively between April and November, and these viruses are the principal causes of meningoencephalitis in the summer and fall. Arboviruses are transmitted by an arthropod vector and, therefore, diseases caused by arboviruses occur only when the vector is prevalent.

CLINICALLY DISTINGUISHABLE SYNDROMES

Viruses produce certain illnesses in children that are so characteristic that they may be diagnosed without any other studies. Such diseases as measles and chickenpox are so familiar to the experienced physician caring for children that there is seldom any question about the reliability of clinical diagnosis. Other diseases, caused by viruses easily recognized clinically, but which may not be as familiar as the childhood diseases, are described in the following section.

Ocular Infections

Viruses that are recognized as important causes of ocular infections are herpes simplex, varicella-zoster, vaccinia and many adenovirus serotypes. Each causes conjunctivitis, which is frequently part of a primary infection or a complication of the primary infection. Typically the ocular manifestations include pain, photophobia, excessive tearing, redness and exudate. Occasionally the infection spreads to involve the lids and is associated with preauricular lymphadenitis. These infections are most often self-limited, and only symptomatic therapy is required.

Keratoconjunctivitis.—Epidemic keratoconjunctivitis is caused by adenovirus 8. The incubation period is thought to be 5–7 days. The disease begins with the sudden onset of photophobia, excessive tearing with redness, and edema of the conjunctiva. Preauricular adenitis usually develops within several days, and the nodes are tender. The disease is initially unilateral but, as it progresses, both eyes may be involved. The conjunctivae have a hobnail appearance, and there may be superficial infiltration of the cornea. Discharge is serous or mucoid. In some patients the corneal infiltrates may ulcerate and these ulcerations may be persistent during the acute phase. In a significant proportion of patients with epidemic keratoconjunctivitis membranes develop and may require surgical removal. Superficial inflammatory corneal opacities are seen and may be persistent. Scarring of the conjunctiva, usually asymptomatic, also occurs.

Epidemic keratoconjunctivitis caused by adenovirus 8 may be acquired in the ophthalmologist's office, and many patients report a recent visit to the eye doctor a few days prior to onset of the infection. These infections can be prevented by meticulous hand-washing and sterilization of instruments.

Herpetic keratitis.—Herpetic keratitis is an important disease because of its frequency and because in the United States it is the most important corneal disease leading to loss of vision. It may occur as a primary disease or in association with other infections. It has a strong tendency to recur, with an over-all recurrence rate of 25%. Some physicians believe that the virus remains latent in the sensory nerves of the cornea and becomes activated by a variety of precipitating factors. The virus frequently is found in the lacrimal gland, and virus is shed frequently in the absence of disease.

The corneal lesion has a characteristic branching dendritic appearance, with corneal clouding and loss of visual acuity (Fig. 1). There is no pain and examination shows corneal sensation to be lost. Clinical diagnosis can be made with a high degree of reliability.

Herpes simplex virus may be recovered from epithelial scrapings or tears. Recurrent infections lead to stromal involvement, and loss of visual acuity is the rule. Every patient with herpes keratitis should be

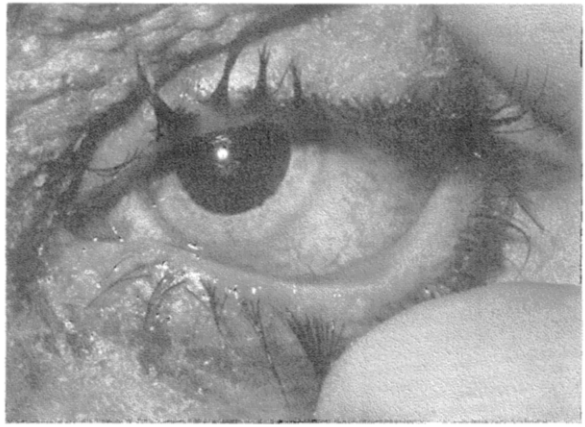


FIG. 1.—Herpetic keratitis. Note clouding of the cornea and marked conjunctival injection. In order to see the dendritic lesion, higher magnification must be used. The lid margins also are involved.

under the care of an experienced ophthalmologist. Treatments include chemotherapy, steroids, curettage, cauterization and cryotherapy.

Even with the best of care the risk of residual damage is great, and, with recurrent infections, spontaneous healing occurs in no more than 10% of patients.

Topical steroids without concomitant chemotherapy are contraindicated in herpes infections of the eye. The most practical approach dictates that topical steroids, with or without antibiotics, should never be used in the eye until the possibility of herpes simplex virus infection is excluded.

UPPER RESPIRATORY TRACT INFECTIONS

Respiratory infections are among the most common infections occurring in children, and viruses are the usual causes. Bacterial upper respiratory infections are relatively uncommon, but it is of practical importance to recognize these infections since they are treatable with antibiotics. Treatment of nonbacterial upper respiratory infections is symptomatic. An anatomic and etiologic classification of upper and lower respiratory infections is presented in Table 2.

Upper respiratory infections caused by viruses sufficiently characteristic to permit recognition clinically include herpangina, herpetic gingivostomatitis and herpes labialis.

HERPANGINA.—Herpangina, or summer sore throat, is a clinically recognizable syndrome caused by several serotypes of Coxsackie A viruses. Herpangina is a common cause of sore throat in children and is seen during the warm months in temperate climates. The onset is abrupt and begins with fever. Anorexia usually is present, along with

TABLE 2.—ETIOLOGIC CLASSIFICATION OF COMMON VIRAL RESPIRATORY TRACT INFECTIONS

- Upper Respiratory Tract
  - Rhinitis
    - Adenoviruses
    - Enteroviruses
      - ECHO
      - Coxsackie A and B
    - Influenza
    - Parainfluenza
    - Respiratory syncytial
    - Rhinoviruses
  - Tonsillitis and/or pharyngitis
    - Adenoviruses
    - Coxsackie
    - Infectious mononucleosis
    - Influenza
    - Parainfluenza
    - Respiratory syncytial
    - Rhinoviruses
    - Herpes simplex
  - Otitis media, acute
    - Viruses infrequently isolated from middle ear
  - Sinusitis
    - Viruses infrequently isolated from sinuses
- Lower Respiratory Tract
  - Laryngitis-laryngotracheobronchitis (croup)
    - Parainfluenza viruses types 1, 2 and 3
    - Adenoviruses
    - Influenza
    - Respiratory syncytial
    - Enteroviruses
  - Bronchiolitis
    - Respiratory syncytial
    - Parainfluenza
    - Adenoviruses
    - Influenza
    - Rhinoviruses
  - Pneumonia
    - Respiratory syncytial
    - Parainfluenza
    - Influenza
    - Adenoviruses
    - Rhinoviruses
    - Miscellaneous
      - Varicella
      - Rubeola
      - Cytomegalovirus

complaints of sore throat and dysphagia. Vomiting, headache and abdominal pain are not uncommon. Examination early in the course of the disease reveals erythema of the throat, sometimes with mild edema. Early on, the appearance of the throat is not characteristic, but after 1 or 2 days characteristic small papules or vesicles, with a red areola and measuring about 2 mm in diameter, are recognized on the anterior pillars, on the margins of the soft palate, on the uvula and less commonly on the tonsils and posterior pharyngeal wall. These papular or vesicular lesions ulcerate within 24–48 hours and at this time are so characteristic that they are clearly diagnostic. The punched-out superficial ulcers usually are confined to structures posterior to the anterior pillars. Cervical lymphadenopathy is not common, and the nodes, when present, are small and nontender.

Early in the disease the leukocyte count may show neutrophilic predominance, but at the time that ulcerative lesions are seen, the leukocyte count is normal or low. Throat culture reveals only normal flora.

Treatment is symptomatic and the disease characteristically runs its course in 5–7 days. Complications are uncommon.

HERPETIC GINGIVOSTOMATITIS.—Herpetic gingivostomatitis usually is a primary infection with herpes simplex virus, type 1. This infection is seen most commonly under the age of 3 years, though it may occur in children of all ages and, rarely, in adults. After an incubation period of 3–12 days, the disease begins with fever, and after 1–2 days the patient complains of sore throat. Shortly thereafter vesicles may be found to involve the mucosa of the mouth. The oral mucous membranes are often generally erythematous prior to the development of vesicles, which progress to ulcers, and the anterior cervical lymph nodes become enlarged and tender. Fever increases, and necrotic ulcers may be seen on the posterior pharyngeal wall, tonsils, tonsillar pillars, soft palate, tongue, buccal mucosa and gingivae. The gingivae are swollen and friable and bleed easily. The odor of the breath is characteristically quite foul, and maintenance of oral hygiene is difficult because of pain. Persistence of fever, with temperatures up to 105° F, and inability to maintain adequate fluid intake often lead to dehydration, which may require hospitalization for intravenous fluid therapy.

Duration of the disease is about 10–14 days. Fever subsides by lysis, and the ulcerative lesions, which have been excruciatingly painful, become painless and heal rapidly.

Complications are uncommon. Herpetic lesions may be found elsewhere on the body and may result from hematogenous dissemination or from direct inoculation (Fig. 2). Encephalitis has not been reported as a complication.

Diagnosis seldom presents any difficulty. Early on, prior to the appearance of ulcers, streptococcal pharyngitis may be suspected. The lesions of herpangina usually are confined to the structures posterior

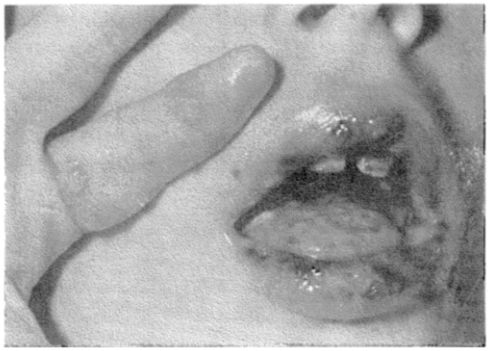


FIG. 2.—Typical appearance of severe herpetic gingivostomatitis. Note lesions on the fingers, the result of direct inoculation or hematogenous spread. (From Haynes, R. E.: The spectrum of *herpes simplex virus* infections in children, South Med. J. In press.)

to the anterior tonsillar pillars. Aphthous stomatitis seldom is associated with fever, and the number of ulcers usually is 10 or less.

Treatment is symptomatic and includes attempts to maintain good oral hygiene. Hydration usually can be maintained by frequent offering of bland liquids. In some cases the judicious use of analgesics or sedatives may be necessary to keep the patient comfortable and to permit the intake of adequate fluids to maintain hydration.

The patient with herpetic gingivostomatitis excretes large quantities of virus, and other members of the household may acquire the infection. Young infants are peculiarly susceptible to herpes infections, and exposure should be avoided when possible.

HAND-FOOT-AND-MOUTH DISEASE.—Hand-foot-and-mouth disease originally was associated with Coxsackie A-16, but it is probably caused by other Coxsackie A viruses as well. It occurs most frequently in preschool age children during the warm months, often in epidemics. Fever (usually low grade), headache, anorexia, malaise and sore throat are the common manifestations. Gastroenteritis may occur. The typical oral lesion is a vesicle surrounded by a red areola. The vesicles rupture, leaving sharply punched-out, superficial ulcers, which are found in any part of the mouth or pharynx, the border of the tongue being a common location. The total number of lesions usually is 10 or less. A maculopapular rash involving the hands and feet also is seen. Superficial vesiculopustular oval lesions, up to 5 mm in diameter and surrounded by a red areola, develop on the hands and feet. The number of lesions usually is 10 or less (Fig. 3). The usual duration of the disease is 5–7 days, and complications are unusual.

HERPES LABIALIS.—Recurrent herpes labialis usually is caused by herpes simplex virus (HSV), type 1. This infection occurs in all age groups and is precipitated by multiple factors such as colds, fever,

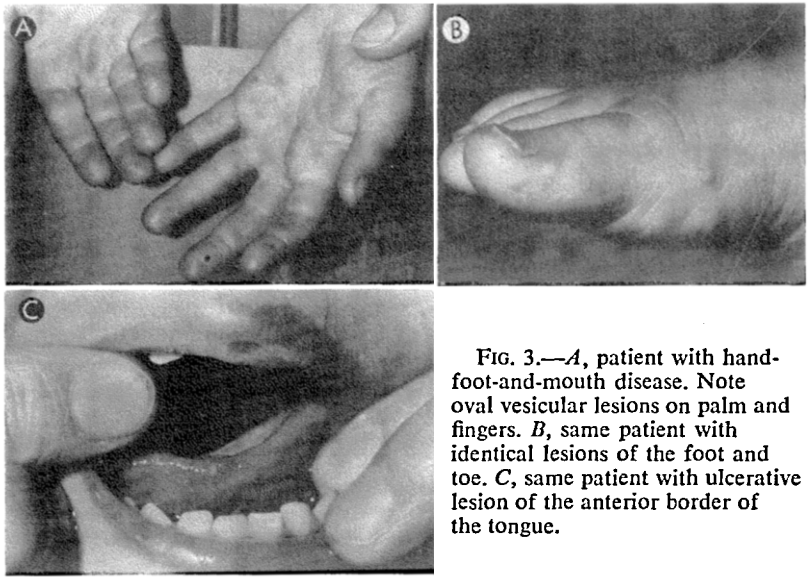
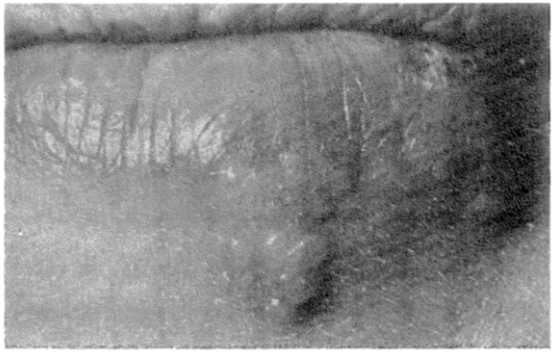


FIG. 3.—*A*, patient with hand-foot-and-mouth disease. Note oval vesicular lesions on palm and fingers. *B*, same patient with identical lesions of the foot and toe. *C*, same patient with ulcerative lesion of the anterior border of the tongue.

exposure to sunshine, menstruation, emotional upsets and certain bacterial infections caused by pneumococci and meningococci. The lesions may occur sporadically or on a regular basis.

The lesions most commonly begin at the vermilion border of the lower lip as an erythematous patch, which later becomes vesicular. The lesions may coalesce to form a cluster involving both the adjacent skin and mucosa (Fig. 4). After several days the loculated lesions rupture, produce a straw colored crust, which also may be hemorrhagic. The lesions are painful and frequently are associated with pain-

FIG. 4.—Typical appearance of herpes labialis with a cluster of vesicular lesions at the vermilion border. (From Haynes, R. E.: The spectrum of *herpes simplex virus* infections in children, South. Med. J. In press.)



ful regional adenitis. The usual duration is 7–10 days, and the lesions heal without scar formation. No effective prophylactic or therapeutic measures are known.

Lower Respiratory Tract Infections

The etiologic diagnosis of lower respiratory tract infections in children is rarely established and the criteria used to make a presumptive etiologic diagnosis are based on epidemiologic studies that have associated viral agents with clinical infectious syndromes. Lower respiratory infections caused by viruses sufficiently characteristic to permit recognition clinically include croup and bronchiolitis.

Croup.—Croup is a nonspecific term indicating upper airway obstruction and can be secondary to foreign body aspiration, diphtheritic membrane, *Haemophilus influenzae* type b epiglottitis or viral laryngotracheitis. Children with viral croup have clinical manifestations that usually allow easy identification. The children are generally under 3 years of age, have had a preceding upper respiratory tract illness with low grade fever, are not toxic and have moderate leukocytosis. Croup is characterized by a distinctive cough that is very harsh, with a barking quality, and usually is more intense at night. The duration of the illness is usually 3–4 days, although it may persist for 7–10 days. The period of most severe respiratory distress is 48 hours or less.

There is tremendous variability in the severity of viral croup, and not all children have the mild benign course described. Some children have a more progressive form, which can be as severe as *H. influenzae* epiglottitis and may require either tracheostomy or endotracheal intubation.

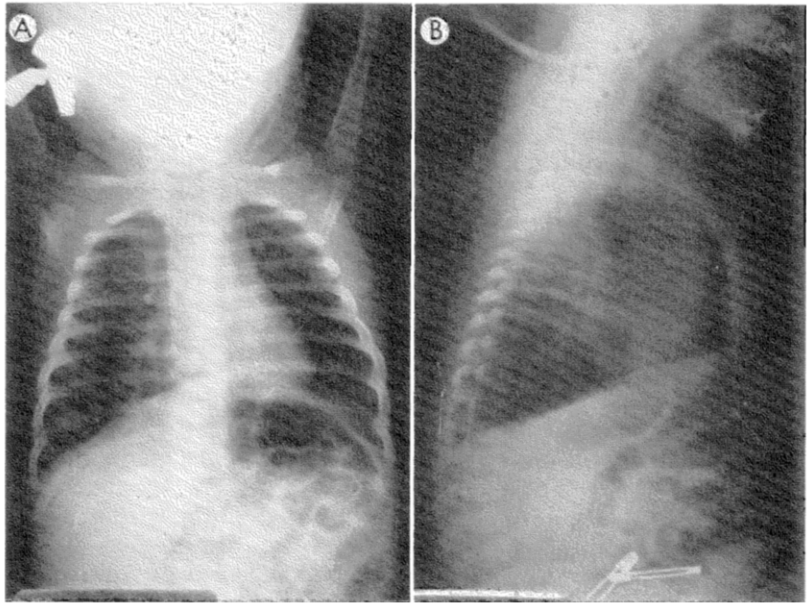
The parainfluenza viruses most frequently are associated with viral croup, and these agents infect the larynx and produce swelling and inflammation of the true and false cords. This leads to upper airway obstruction and the resultant signs and symptoms. In some children with recurrent episodes of viral croup, hypersensitivity may play a role in the pathogenesis.

Because of the relatively greater severity of *H. influenzae* epiglottitis, it is extremely important to be able to distinguish epiglottitis from other causes of croup. Epiglottitis is most common in children 2–8 years of age and is characterized by a very sudden onset. The usual interval from the first sign or symptom to significant inspiratory stridor is less than 12 hours. There is a history of sore throat and dysphagia. When seen by a physician, the children appear toxic, acutely ill, agitated, drooling and holding the neck in a hyperextended position. The breathing is stridulous, but not as noisy as that of a child with viral croup. The definitive diagnosis is made when the enlarged, edematous, bright red epiglottis is observed by an experienced physician under controlled conditions.

BRONCHIOLITIS.—Bronchiolitis, a viral infection of the lower respiratory tract, is a disease of the very young. Most children are under 1 year of age. It is characterized by preceding nonspecific upper respiratory tract symptoms with low grade fever and the subsequent development of a brassy cough and moderate-to-severe respiratory distress. On examination, the child is tachypneic, the anterior posterior diameter of the chest is increased, the expiratory phase of respiration is prolonged and there are suprasternal and intercostal retractions. On auscultation of the chest, wheezes, rhonchi and/or rales are present in all lung fields. Roentgenograms of the chest show hyperinflation, flattened diaphragm and air bronchogram (Fig. 5). The heart rate usually is increased, and the liver edge is easily palpable below the costal margin. In most cases this does not represent heart failure, and the apparent hepatic enlargement is caused by hyperinflation of the chest and depression of the diaphragm.

The viruses associated with bronchiolitis are RSV, parainfluenza and adenoviruses. The RSV most often is associated with bronchiolitis in children under 6 months of age and may represent a hypersensitivity reaction to the RSV with RSV antibody. The relationship of bronchiolitis in infancy to the development of asthma in older children is not

FIG. 5.—*A*, roentgenogram of the chest shows marked hyperinflation. Air bronchograms also are seen in the peripheral lung fields. *B*, lateral view shows depression of the diaphragm and increase in anterior-posterior diameter of the chest.



clear. We do know, however, that from 25–56% of children who have had bronchiolitis will have recurrent wheezing episodes 2–7 years after the initial episode of bronchiolitis. The RSV also appears to be able to precipitate wheezing in asthmatic children. Adenovirus has been associated with a severe necrotizing form of bronchiolitis, which has a high morbidity and mortality rate.

MUMPS

Mumps virus causes multisystem diseases. Mumps parotitis is clinically distinguishable and the complications of mumps are recognizable when associated with mumps parotitis. Mumps is an acute contagious infection manifested by painful swelling of the parotid glands. Other salivary glands, the central nervous system (CNS), pancreas and testes may be involved.

EPIDEMIOLOGY.—Mumps is a widespread disease of children, endemic all over the world. It is spread by droplets of saliva. Virus may be found in saliva up to 7 days before and 9 days after salivary gland swelling. Virus is present in saliva of patients with orchitis or meningoencephalitis without apparent salivary gland swelling.

Subclinical infection, detectable by antibody response, is common in mumps. The disease occurs throughout the year but the highest incidence is in winter and early spring.

PATHOGENESIS.—The virus multiplies first in the cells of the respiratory tract, then invades the blood stream and localizes in salivary glands and other areas such as the CNS, testes and pancreas, causing inflammatory responses.

CLINICAL MANIFESTATIONS.—The incubation period is 14–24 days. Onset of illness usually corresponds to the pain and swelling of one or both parotid glands, with soft tissue swelling. Enlargement of the salivary glands is more readily detected by sight than by palpation. Swelling is seen anterior, posterior and inferior to the ear, with the ear lobe in the middle of the swelling. The angle of the mandible is not palpable. Swelling is found both above and below the inferior border of the mandible, whereas in cervical adenitis swelling is found only below. Early on, the swelling is soft but, as swelling progresses, the entire area becomes indurated (Fig. 6). Redness often is seen around the opening of Stensen's duct. Fever usually is present. Submandibular or sublingual glands may be involved, with or without parotitis. Presternal edema is present in about 10% of patients. Fever and swelling usually disappear within 5–7 days.

NEUROLOGIC MANIFESTATIONS.—Mumps virus is the single most common cause of meningoencephalitis, if the cases occurring over at least a 5-year period in a given geographic area are counted. Mumps meningoencephalitis may be preceded, accompanied or followed by involvement of the salivary glands. On the other hand, meningoencephalitis may be the sole manifestation of mumps infection.

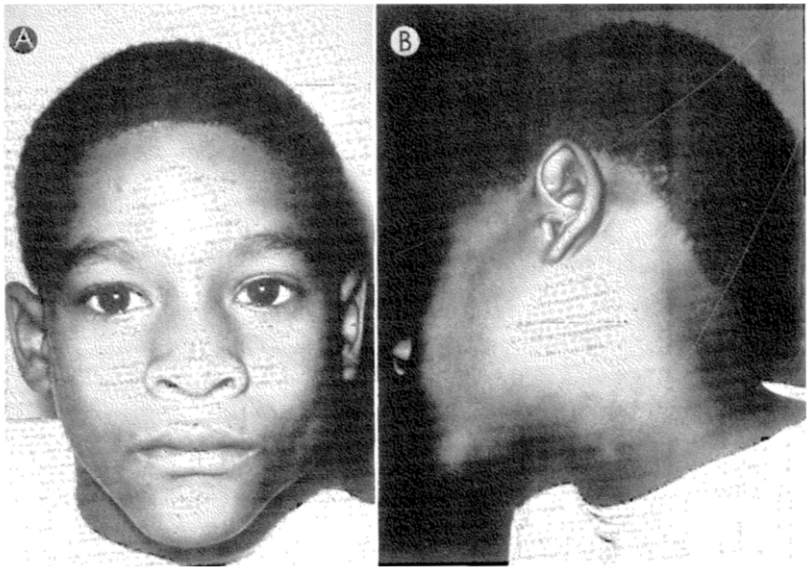


FIG. 6.—*A*, patient with mumps demonstrates lateral displacement of the ear lobe. *B*, in this view the swelling is seen anterior, inferior and posterior to the ear, with the ear lobe in the center of the swollen area. Note swelling both above and below the mandible.

ORCHITIS.—Orchitis is a very rare complication before puberty but occurs in about 20–25% of patients after puberty. The incidence of sterility after bilateral orchitis is unknown, but there is evidence to suggest that mumps orchitis is an unlikely cause of sterility. Symptoms of orchitis consist of pain, tenderness and swelling. Pain is the earliest symptom and occurs 5–10 days after the onset of salivary gland involvement. The testicular swelling and tenderness last an average of 4 days.

PANCREATITIS.—Epigastric pain and vomiting are the common manifestations of pancreatitis. Elevation of serum amylase is present with or without pancreatitis when there is salivary gland involvement and is therefore not indicative of pancreatitis. Other complications such as nephritis, thyroiditis, myocarditis, deafness, arthritis and thrombocytopenic purpura are rare.

The association of maternal mumps infection and endocardial fibroelastosis in the fetus has been postulated but not proved.

DIAGNOSIS.—When parotitis is present, the diagnosis presents no difficulty. Inflammation of salivary glands is associated with elevation of serum amylase. Serum amylase levels usually are normal in patients with primary meningoencephalitis. When meningoencephalitis is not accompanied by parotitis, the diagnosis must be based on isolation of

the etiologic agent or demonstration of significant rises in the titer of complement fixative (CF) or hemagglutinin-inhibiting (HI) antibodies in sera collected during the acute and convalescent phases of illness.

Isolation of mumps virus in cell cultures from the cerebrospinal fluid (CSF) of patients with mumps meningoencephalitis is easily accomplished. Virus isolation is also possible from saliva and urine. Serologically the diagnosis of mumps infection is possible on the basis of demonstration of CF antibodies against both V (viral) and S (soluble) antigens in a single serum specimen. In the acute stages of the disease, serum contains antibodies against S antigen but a negligible antibody titer against V antigen. During convalescence both antibodies are demonstrable at high level but in subsequent months they decrease, S at a faster rate than V. This particular pattern of antibodies permits a diagnosis of mumps infection at various stages of illness.

TREATMENT AND PROPHYLAXIS.—Treatment usually is symptomatic.

Although the illness usually is not severe and sequelae are rare, orchitis occurs in approximately 20% of postpubertal males and constitutes a reasonable justification for prophylaxis. Live attenuated mumps vaccine, which is of proved efficacy, is now recommended for this purpose. Highest priority should be placed on the immunization of prepubertal adolescent and adult males with a negative history of pumps.

Hyperimmune globulin and inactivated vaccines are not as effective and are not recommended.

PRESUMPTIVELY DIAGNOSED SYNDROMES

In addition to the clinically recognizable diseases caused by viruses, there are many illnesses in which the viral etiology can be strongly suspected. The use of selected laboratory tests usually available to most physicians will yield information that will support the clinical impression. In most instances the course of the illness will further support the probable viral etiology.

The following section will be devoted to a discussion of these diseases.

RESPIRATORY TRACT INFECTIONS

THE COMMON COLD.—The common cold is a self-limited infection seen in all seasons, the peak incidence being in winter. In adults rhinoviruses probably account for 25% of colds. In children rhinoviruses are less commonly implicated, whereas other viruses, particularly RSV, parainfluenza virus and adenovirus, are more common etiologic agents.

The primary symptom is nasal discharge; other symptoms are variable. Temperature exceeding 101° F is unusual. Constitutional symp-

toms such as headache, myalgia, sore throat and anorexia may be present, particularly when the nasopharynx is involved.

Examination reveals low grade fever, congestion of the nasal mucosa and a nasal discharge, which may be either mucoid or mucopurulent. When the pharynx is involved, there usually is diffuse erythema of the pharynx, and the cervical lymph nodes are minimally enlarged and usually nontender.

In infants with upper respiratory infections nasal obstruction may develop sufficient to produce respiratory distress, since in early life they are obligate nasal breathers. In these patients relief of nasal obstruction by gentle suctioning after instillation of sterile normal saline or the judicious use of decongestants such as 0.25% phenylephrine may result in dramatic relief of respiratory distress. The use of decongestants orally also may give symptomatic relief.

The intimate relationship of the middle ear and paranasal sinuses with the nasopharynx predisposes to the infection of these structures when the openings become obstructed by mucosal edema or secretions. The lower respiratory tract also may be involved by extension of these infections.

ADENOVIRAL PHARYNGITIS.—Multiple serotypes of adenovirus have been associated with pharyngitis, adenovirus 3 being the most common. The clinical picture produced by different serotypes is similar. Adenoviral pharyngitis has been described in epidemic form among military recruits and occurs in children of all ages. The incubation period is 5–7 days. The illness develops over a period of several days and is characterized by fever and sore throat. Anorexia, nausea, headache, hoarseness and cough are frequent, and often conjunctivitis is a prominent finding. On examination, the throat may be red, with lymphoid hyperplasia, most easily recognized on the posterior pharyngeal wall. Exudate may be present either on the posterior pharyngeal wall or on the tonsils. Exudate may be superimposed on the lymphoid follicles or the tonsils, but is sparse and occurs as small, grayish white follicles. Inflammation of the nasal mucosa often is present. Conjunctivitis may be either unilateral or bilateral and is seldom severe. The palpebral conjunctivae most often are involved and are follicular in appearance. There usually is excessive tearing, and some purulent discharge is not uncommon. When conjunctivitis is present, preauricular lymphadenopathy may be recognized. Cervical lymphadenopathy may be present, but it appears later than with streptococcal pharyngitis, and the nodes are seldom more than moderately enlarged and are either nontender or only mildly tender.

The complete syndrome has been referred to as pharyngoconjunctival fever. Conjunctivitis, when present, is helpful in diagnosis. The leukocyte count usually is within normal limits. The primary responsibility is to exclude streptococcal pharyngitis, and this is best accomplished by throat culture, which should yield only normal flora.

The natural course of the illness seldom extends more than 5–7

days. Fever fluctuates, with temperatures up to 104° F, and there is a gradual disappearance of symptoms, with subsidence of the acute inflammatory changes in the pharynx and conjunctivae.

Treatment is entirely symptomatic. Acetylsalicylic acid or acetaminophen may be used for the control of fever. Conjunctivitis seldom requires therapy, though Collyrium may be used.

Complications such as otitis media, sinusitis or lower respiratory tract infections may follow. Decongestants, with or without antihistamines, are often used in an effort to prevent complications, but proof of efficacy is lacking.

ACUTE LYMPHONODULAR PHARYNGITIS.—This disease, recognized in children, is caused by Coxsackie A-10. Symptoms include fever, headache and sore throat. The disease is recognized by the discrete nodular lesions of the uvula, anterior pillars and posterior pharyngeal wall. The nodules are covered by a whitish to yellowish exudate, and they do not ulcerate. The disease usually persists for about 1 week. Treatment is symptomatic, and complications are rare.

PNEUMONIA.—The clinical diagnosis of viral pneumonia usually is made by excluding bacterial and Mycoplasma pneumonia, since the diagnosis of viral pneumonia is difficult to establish with certainty.

The etiologic diagnosis of bacterial pneumonia is hindered because it is difficult to obtain specimens and culture from the site of pathology. All diagnostic procedures short of lung biopsy or lung aspiration are indirect diagnostic technics. Blood cultures are helpful when positive but only 20–30% of patients have positive blood cultures. Sputum specimens are difficult to obtain in young children and, if collected, are contaminated with saliva. Nasopharyngeal and throat cultures are of little value because lower respiratory tract pathogens are found in the upper respiratory tract of patients without disease. The recovery of a pneumococcus, for example, from a nasopharyngeal culture of a child with pneumonia indicates colonization of the upper respiratory tract with pneumococcus but it does not establish the pneumococcus as the cause of pneumonia.

The clinical guidelines used in the diagnosis of bacterial pneumonia have been established from the study of two groups of patients. The first group comprises those with presumed pneumococcal pneumonia. The sputum contains polymorphonuclear cells and gram-positive, lancet-shaped diplococci. The patient usually responds promptly to penicillin therapy. The second group of patients comprises those with positive cultures from blood, lung tissue or empyema fluid. The guidelines allow separation of pneumonia into two general categories: bacterial and nonbacterial.

Bacterial.—Pneumococcal pneumonia is the most frequent bacterial pneumonia in children. The frequency of pneumonia caused by *H. influenzae* is not well established. Pneumonia caused by *Staphylococcus aureus* occurs most frequently during the neonatal period, during the

first year of life and in patients with a predisposing factor. Common predisposing factors include underlying diseases such as malignancy, measles, influenza and varicella. Other factors are hospital exposure, antibiotic therapy, staphylococcal infections in the patient and exposure to staphylococcal infections in the environment.

The clinical picture of bacterial pneumonia is characterized by toxicity and respiratory distress, manifested by tachypnea, tachycardia, alar flaring and use of the accessory muscles of respiration. These signs usually are sudden in onset, with progression of severity. The leukocyte count is markedly elevated, with a predominance of polymorphonuclear cells. Physical examination of the chest, particularly in younger children, reveals no abnormalities, and evidence of bronchospastic disease usually is absent. Roentgenograms often reveal pleural effusions, lobar consolidation and pneumatoceles. Blood cultures are positive in 30% or more of patients. Staphylococcal pneumonia tends to be rapidly progressive and destructive, even with adequate antibiotic therapy, whereas pneumococcal pneumonia responds rapidly to penicillin therapy, in the absence of effusions, and most patients, treated early, are asymptomatic in 24 hours.

Nonbacterial.—In the child with nonbacterial pneumonia, the clinical picture differs. Onset is gradual, and the pneumonia usually is preceded by several days of nonspecific upper respiratory tract symptoms, with a gradual progression of respiratory distress and cough. On physical examination, there often are numerous rales and rhonchi and occasionally wheezing. A good general rule is that patients with nonbacterial pneumonia have more abnormal physical findings in their chest than children with bacterial pneumonia. The child is relatively less toxic and the leukocyte count is usually less than 15,000/mm^3. Nonbacterial pneumonia can be localized to one lobe or may involve all lobes in a bronchopneumonic type of distribution. Pleural fluid accumulation is extremely rare. Antibiotic therapy produces no significant improvement in 24–48 hours, but there usually is neither clinical nor roentgenographic evidence of progression of the pneumonia.

In the child with pneumonia, the exclusion of bacterial pneumonia does not verify the diagnosis of viral pneumonia because Mycoplasma pneumonia has clinical and laboratory features that are indistinguishable from viral pneumonia. Mycoplasma pneumonia, however, frequently occurs in epidemics and among children of school age or older. The serologic tests that are readily available for the diagnosis of Mycoplasma pneumonia are the cold agglutinin, which is nonspecific, and the Mycoplasma CF test, which is specific. The cold agglutinin test is positive in most patients with Mycoplasma pneumonia and provides presumptive evidence for the diagnosis. Since the Mycoplasma CF test is specific, it can provide epidemiologic data on the prevalence of Mycoplasma infections in the community.

The diagnosis of specific viral pneumonias such as influenza can be

strongly suspected during an epidemic, but the diagnosis of viral pneumonia is made by the recovery of a virus from the site of pathology.

INFLUENZA.—Influenza is an acute respiratory infection caused by one of the influenza viruses, types A, B or C. Influenza A, B and C are myxoviruses, subclassified as orthomyxoviruses. These three major types are immunologically distinct, with no cross-immunity.

Epidemiology.—Influenza A and B are responsible for the outbreaks of this disease; influenza C rarely produces clinical disease sporadically and has not been associated with outbreaks.

Major antigenic variations in influenza A have occurred during the past few decades. On the basis of the external antigens, neuraminidase and hemagglutinin, four major subtypes of influenza A have been recognized: A/swine, prevalent from 1917 to the 1930s; influenza A, from the 1930s to mid-1940s; influenza A, from 1947 to 1957; influenza A_2, from 1957 to 1968–69 and A_2 Hong Kong strain, from 1969 to the present time. The antigenic variation has also occurred in the surface antigens of influenza B virus. This is especially demonstrated in recently isolated influenza B viruses. These antigen changes are not major shifts and are not of sufficient magnitude to warrant distinct subtypes. The major antigenic shifts of influenza A viruses are of the utmost epidemiologic importance. Once this shift occurs, new virus replaces the earlier strains and makes the existing vaccine ineffective, and the individual immune to the previous virus is susceptible to the new strain.

After the introduction of a new major strain, pandemics and epidemics of influenza sweep rapidly through susceptible populations, causing considerable economic loss and high morbidity and mortality, especially in the elderly and very young. As the population acquires immunity to the new virus variant, the epidemics decline in magnitude until the majority of the population is immune (usually in a span of 10–12 years). This immunity inhibits the survival of the virus; therefore, it will be replaced by a new variant. The emergence of a new variant strain makes the prevention and control of this disease very difficult. These viruses are spread by direct contact via respiratory secretions. The attack rate is highest in school age children, presumably due to greater risk of exposure. In temperate climates there is a definite seasonal incidence, with highest attack rates in the winter months.

Symptoms and signs.—The incubation period is 1–3 days. In epidemics a spectrum of clinical disease has been observed. The majority of cases are asymptomatic and are recognized only by viral isolation or antibody response. The onset in symptomatic cases is abrupt, with malaise, myalgia, headache, chills, fever, cough, substernal burning, nasal discharge and sore throat; combinations of the above symptoms are found in varying intensity. The total duration of uncomplicated disease is about 2–4 days. Many patients feel debilitated for some time

after recovery. The most common complication, which is responsible for the majority of deaths in epidemics of influenza, is pneumonia. Pneumonia may be caused by influenza virus or secondary bacterial agents. This complication is frequently encountered in children with heart disease and in elderly patients with chronic lung disease.

The organisms most commonly responsible for secondary bacterial pneumonia are *Diplococcus pneumoniae* and *Staphylococcus aureus*. Pneumonia caused by influenza virus is associated with dyspnea, tachycardia and productive cough, often with bloody sputum. In severe cases cyanosis may be present, and x-ray shows diffuse bronchopneumonia. An epidemiologic association between epidemic influenza B disease and Reye's syndrome has been noted.

Treatment.—Treatment consists of bed rest, analgesics and fluids. Antibiotics are of no value for the treatment of uncomplicated influenza. Secondary bacterial pneumonia should be treated with appropriate antibiotics.

Prevention.—Illness may be prevented by immunization with influenza vaccine and chemotherapy.

Vaccine.—The influenza vaccines presently available are bivalent, containing both the current A and B antigens. The virus for production of the vaccine is propagated in eggs and inactivated. The bivalent vaccine used at the right time affords 75–80% protection against clinical influenza. The vaccine is given parenterally and is more effective in producing circulating antibody than secretory immunoglobulin A (IgA) in the respiratory tract. The duration of protection is brief, and repeated boosters are required, usually on an annual basis. The minor antigenic changes that occur in influenza A viruses from season to season make the current vaccine less effective, but the reduction of vaccine efficiency is minimal. The vaccine is ineffective when there is a major antigenic shift between vaccine and epidemic virus. This significant property of the virus, "the antigenic lability," requires preparation of a new vaccine containing the most recent mutant strains. Influenza is a self-limited disease in an otherwise healthy child or adult and, since the protection afforded by vaccine is transient, vaccination against influenza is not recommended routinely. Vaccination is recommended for persons over the age of 65 and those with underlying bronchopulmonary, cardiovascular or renal disease.

Studies with live attenuated aerosolized vaccine virus in which no parenteral injections are necessary and which stimulate a superior IgA response are being carried out. Additional information about these vaccines and the purified subunit vaccines containing influenza hemagglutinins will be of great interest.

Chemotherapy.—Amantadine, a synthetic antiviral agent, has been shown to be effective for prevention of influenza A infection but ineffective for prevention of influenza B infection. It is thought to prevent penetration of the virus into the cell. This drug must be adminis-

tered prophylactically for as long as the threat of exposure exists. This, along with its toxic effects, limits the use of the drug in the general public. Drug in high doses may cause CNS toxicity such as hyperexcitability, tremors, slurred speech, ataxia, psychotic reactions and convulsions.

Viral Myocarditis

Viral myocarditis is often suspected in infants and children, but the diagnosis is difficult to establish with certainty. Viruses associated with myocarditis in children include Coxsackie, ECHO, adenovirus, varicella-zoster, Epstein-Barr (E-B), mumps, rubella, rubeola, cytomegalovirus (CMV) and polio. Because of the multiple etiologic agents associated with viral myocarditis and the ever-present possibility of rheumatic myocarditis, an unequivocal diagnosis is difficult. There are, however, several clinical diagnostic points that are useful in making a presumptive etiologic diagnosis.

Coxsackie B viruses are the most frequent cause of viral myocarditis and produce clinical features that can be easily identified. Transmission of the virus to the infant can occur either across the placenta or by the oral-fecal route. Evidence for transplacental transmission of the agent comes from studies in which the Coxsackie virus has been recovered from stillborn infants and from studies in which infants became ill within hours after delivery. The virus has not been isolated from the placenta, nor has histologic evidence of placental infection been demonstrated, Coxsackie B virus frequently is present in stool specimens of infected patients, and therefore fecal contamination of the vagina, uterus and fetoplacental membrane could produce infection in the infant by direct extension.

The reports of 48 children with Coxsackie B virus myocarditis have been reviewed to describe the clinical and epidemiologic features. The neonatal form is the most common and accounts for 29 of 48 patients reviewed. Coxsackie B myocarditis occurring in the neonatal period has several distinguishable clinical features. There is often evidence of Coxsackie B virus infections in the community or in the mother. The mothers of eight of 18 infants with myocarditis in the first week of life either had coryza, fever and/or pleurodynia. The disease usually develops in the first week of life (18 of the 29 patients). The signs and symptoms of neonatal myocarditis are similar to those of neonatal sepsis and include fever, lethargy, irritability, seizures, tachypnea, tachycardia, hepatosplenomegaly and cardiomegaly. The most constant clinical feature, however, is congestive heart failure. Systems other than cardiovascular frequently are involved, and 10 of the 29 patients had either meningoencephalitis, hepatitis or pneumonia. The prognosis is poor and the reported fatality rate for neonatal Coxsackie B myocarditis is 79%.

Coxsackie B viral myocarditis in older children is more difficult to differentiate from other types of myocarditis and is clinically indistinguishable from ECHO virus myocarditis; for this reason they will be discussed together. Seasonal factors are important since both Coxsackie B viruses and ECHO viruses are enteroviruses within the picornavirus group of RNA viruses and generally produce disease in warm weather. Of 36 patients with enteroviral myocarditis, in only nine did their illness develop between November and March.

The illness in these children is biphasic. The first phase usually is characterized either by nonspecific upper respiratory or gastrointestinal infection, followed a week or 2 later by signs and symptoms of congestive heart failure. Meningoencephalitis may occur at or near the time of the development of myocarditis and has been reported with both ECHO virus and Coxsackie B virus myocarditis. Involvement of both the myocardium and CNS in a child during the summer months is presumptive evidence of enteroviral myocarditis. We have had the opportunity to study the illness of a child with ECHO 3 myocarditis and meningoencephalitis and include the case in detail here to illustrate this clinical manifestation.

CASE REPORT.—A 3-month-old Caucasian boy was admitted because of seizures. The infant had been well until the day before admission when he developed fever and anorexia. On the day of admission he had a 15-minute generalized seizure, which was terminated with administration of diazepam intravenously. Immediately afterward, respiratory arrest occurred. After he was resuscitated, pulse was 180/minute, respirations were 40/minute, and flush blood pressure was 100 mm Hg. There was a soft grade 1 systolic murmur at the left sternal border; the heart sounds were described as muffled. The liver edge was palpable 4 cm below the right costal margin. The chest roentgenogram revealed a markedly enlarged heart. The ECGs showed low voltage in all leads. Serum enzyme studies revealed lactic dehydrogenase activity of 1,800 units/ml and SGOT of 94 units/ml. A heart scan using ^{99m}technetium as pertechnetate revealed a pattern consistent with pericardial effusion. Two weeks later a repeat heart scan was normal. The CSF at the time of admission contained no leukocytes, 28 erythrocytes/cu mm, protein 60 mg/100 ml and glucose 48 mg/100 ml. ECHO virus type 3 was recovered from this specimen and from a second CSF specimen obtained 2 days after admission.

Ventilation was maintained with a Bennett respirator. Congestive heart failure was controlled with oxygen, digoxin and ethacrynic acid. The systolic murmur heard initially disappeared. Aqueous penicillin G, 100,000 units/kg/day, was given intravenously, and kanamycin, 15 mg/kg/day, was administered intramuscularly. Dexamethasone, 2 mg daily, was given during the first 5 hospital days. The patient improved slowly following resumption of spontaneous respirations and was discharged 3 weeks after admission. Chest roentgenograms showed a large cardiac silhouette on the day of admission and a normal sized heart 3 weeks after discharge (Fig. 7).

Adenovirus also has been associated with myocarditis in children less frequently than have enteroviruses. Adenovirus myocarditis has

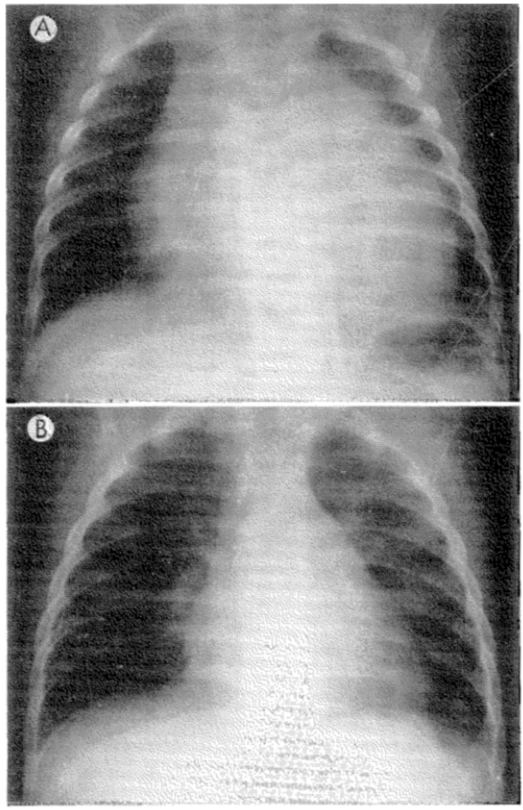


FIG. 7.—*A*, marked cardiomegaly on day of admission. *B*, roentgenogram 6 weeks later. Heart size has returned to normal.

developed in children under 1 year of age and has been associated with infections of both the upper and lower respiratory tracts. The clinical features are nonspecific and are primarily those of congestive heart failure. Other viruses associated with myocarditis are mumps, varicella-zoster, E-B virus, CMV, rubella and rubeola. These viruses produce a rather typical clinical disease, and myocarditis usually is a complication of the primary disease.

The presumptive clinical etiologic diagnosis of myocarditis is dependent upon epidemiologic and clinical data. ECHO and Coxsackie virus infections are most likely to occur during the summer months, whereas the other etiologic agents mentioned can occur at any time of the year. Coxsackie virus myocarditis would be suspected in a neonate with myocarditis and meningoencephalitis or hepatitis, especially if pleurodynia or other Coxsackie B infections are prevalent. ECHO virus myocarditis would be most likely to occur in the summer months

also, but it usually is not associated with neonatal infection. It would be most likely to occur in an older child, either following a nonspecific upper respiratory infection or perhaps in association with meningoencephalitis. Adenovirus myocarditis could occur at any time of the year and would probably be preceded by a nonspecific respiratory tract illness. Diagnostic procedures should include attempts at virus isolation and serologic studies. Unfortunately, the etiologic diagnosis may not be proved, and final diagnosis must be based on clinical criteria alone.

The role of viruses as a cause of myocarditis in children has been clearly established, and in infants viruses are much more important than in older children. It should be borne in mind that rheumatic fever still is the single most important cause of myocarditis in children. Differentiation of rheumatic and viral myocarditis usually presents little difficulty. Rheumatic fever with myocarditis is unusual in children under 3 years of age and usually occurs in association with other rheumatic manifestations and significant murmurs.

Gastroenteritis

Acute infectious nonbacterial diarrhea occurring sporadically or in epidemic form often has been termed "viral gastroenteritis." Although Coxsackie, ECHO and adenoviruses have been associated with gastroenteritis, the majority of cases of nonbacterial gastroenteritis are etiologically unexplained.

Acute infectious nonbacterial gastroenteritis generally is self-limited and is characterized by symptoms such as low grade fever, nausea, vomiting, abdominal cramps and diarrhea. Recent studies indicate that the cause of this disease may be viruses that have not been cultivated but have been identified by electron microscopy in the duodenal mucosa of patients with acute gastroenteritis.

Studies in human volunteers after ingestion of stool filtrate containing Norwalk agent have shown clinical illness and the development of lesions in the mucosa of the proximal small intestine.

Orbiviruses, a group closely related to reoviruses, have been shown to be associated with gastroenteritis in children. These viral particles have been identified in the epithelial cells of duodenal mucosa along with histologic changes of mucosa and depression of disaccharidase activity. Obviously the exact importance of these agents as a cause of gastroenteritis awaits further clarification.

Central Nervous System Infections

Viruses that are frequent causes of acute meningoencephalitis in children are shown in Table 3. Aseptic meningoencephalitis may be described in terms of the CSF findings, which are as follows: leuko-

TABLE 3.—ETIOLOGY OF VIRAL MENINGOENCEPHALITIS

Enteroviruses	
	Polio, types 1, 2 and 3
	ECHO, many serotypes
	Coxsackie A and B, many serotypes
Herpesviruses	
	Herpes simplex
	Varicella-zoster
	Cytomegalovirus
	Epstein-Barr
Mumps Virus	
Arboviruses	
	California encephalitis
	St. Louis encephalitis
	Eastern equine encephalitis
	Western equine encephalitis
Postinfectious	
	Rubeola
	Rubella

cytes, 500 or fewer per cu mm, usually but not necessarily predominantly mononuclear cells; normal glucose and protein content; and a negative smear and culture for bacteria and fungi. Except in neonates, normal values are fewer than 10 leukocytes per cu mm, glucose 40 mg % or approximately two thirds of the serum glucose value, and protein content 40 mg % or less. There are many noninfectious diseases and nonviral infections that may cause these CSF findings. Aseptic meningoencephalitis may be caused by a variety of etiologic agents, and only the pursuit of a specific etiologic agent will avoid delay in the recognition and treatment of diseases that constitute a serious threat to the life and welfare of children.

Mumps virus on a perennial basis is the single most frequent cause of aseptic meningoencephalitis. The disease occurs in all seasons, before, during or after parotitis or without parotitis. The patient may appear quite sick and toxic, and lumbar puncture often is followed by an impressive remission of symptoms.

In temperate climates the enteroviruses are very frequent causes of aseptic meningoencephalitis occurring almost exclusively between April and November. All three types of poliovirus, many ECHO virus serotypes and Coxsackie A and B viruses cause the infection. In general, it is a relatively mild disease and is unassociated with focal neurologic signs. The duration usually is less than a week, and sequelae are rare. Enteroviruses of the same serotype produce simultaneous epidemics of aseptic meningoencephalitis in many widely separated parts of the country. In general, the clinical characteristics of the illness are similar irrespective of the group and serotype of virus, and for practical pur-

poses there is no particular advantage to the identification of the virus beyond recognition that it is an enterovirus. This is true for poliovirus, which often produces a benign CNS illness, though the clinical manifestations may include anterior horn cell disease with asymmetric flaccid paralysis, bulbar disease or encephalitis. Other enteroviruses may rarely cause a polio-like disease with specific neurologic deficit. ECHO and Coxsackie viruses are frequently isolated from the CSF.

HSV is an important cause of CNS infections. The virus probably causes a spectrum of illness in terms of severity and may cause disease in all age groups. Benign aseptic meningoencephalitis caused by HSV is clinically indistinguishable from other meningoencephalitides. Unfortunately, however, HSV also causes a very severe encephalitis, with high case fatality rate, and a high incidence of serious permanent neurologic sequelae among survivors.

The illness occurs in all seasons. The initial symptoms usually are fever, headache and vomiting, followed by rapidly progressive alterations of the sensorium such as lethargy, delirium, semicoma and coma. Focal neurologic signs including cranial nerve palsies, weakness, paresis, abnormal reflexes and focal seizures are common. This severe picture of rapidly progressive neurologic deterioration occurs over a period of 1–3 days. The CSF findings early are typical of those seen with other viral meningitides, but erythrocytes often are found and, as the disease progresses, the CSF pressure rises and the protein content may increase rapidly. The virus is almost never recovered from the CSF. The electroencephalogram reveals delta activity, 2–3 cycles per second, and spike activity concordant with hemiparesis and seizures. Brain scan may show increased uptake, most often in the temporal lobe. The pattern also may resemble the doughnut appearance characteristic of brain abscess, with a central area of decreased uptake surrounded by a circumferential area of increased uptake. Carotid angiography may reveal vascular displacement suggesting a mass lesion such as tumor or abscess.

Diagnosis can be proved only by brain biopsy of the focal area delineated by prior studies. The specimen should be examined for the histopathologic changes consistent with encephalitis, and specifically for the presence of intranuclear inclusion bodies. A specimen should also be inoculated into cell cultures, and in our experience cytopathology characteristic of HSV may be recognized between 18 and 72 hours after inoculation.

The present treatment of herpes encephalitis consists of supportive care, attempts to control intracranial hypertension secondary to cerebral edema, and perhaps chemotherapy. Iododeoxyuridine has been tried with varying reports of efficacy; however, the consensus is that this drug is too toxic for continued trials. A second drug, adenine arabinoside, is being studied, but as yet no data concerning efficacy is available, though preliminary studies do not suggest significant toxicity.

At present, diagnosis is possible only by brain biopsy, a procedure

which, while not without risk, has been carried out in our hospital without serious complications. The severity of herpes encephalitis is such that continued studies with promising chemotherapeutic agents are fully justifiable. In order that the results may be evaluated, diagnosis must be confirmed by biopsy and therapy must be begun prior to the development of irreversible brain damage.

The only arbovirus causing encephalitis in central Ohio is California encephalitis virus. The virus is transmitted to humans by the mosquito, and therefore the disease occurs primarily in the summer and early fall. Fever, headache and vomiting are the initial symptoms, followed by lethargy, disorientation and, in severe cases, semicoma or coma. Seizures occur in about 60% of patients, and after onset the disease tends to be rapidly progressive. Focal neurologic signs such as facial weakness, focal seizures and transient hemiparesis are common. Early on, the disease resembles herpes encephalitis; however, patients with California encephalitis may show improvement after 4–5 days, whereas those with herpes encephalitis show progressive neurologic deterioration.

The CSF findings are characteristic of aseptic meningitis. Electroencephalography shows generalized cerebral dysfunction, with some evidence of focality. Brain scans may be normal or may demonstrate increased uptake suggestive of focal lesions. Diagnosis is based on serologic tests such as the HI or CF.

The duration of illness is usually about 10 days. Most patients recover completely, although some display emotional lability for a period of several months.

The patient presenting with a CNS infection associated with CSF findings compatible with aseptic meningoencephalitis has a disease of variable etiology. The primary responsibility of the physician is to identify treatable diseases. He must consider seasonal factors, history of exposure and immunization history, along with careful documentation of the onset and progression of the illness. Careful physical examination, including a detailed neurologic examination, is essential. Lumbar puncture with opening and closing pressures and determination of the CSF contents also is essential. In particular, the CSF findings should be viewed with suspicion if the cell count is higher than expected or if the protein content is higher or the glucose content lower than expected. A repeat lumbar puncture performed a few hours after the first may be of great value. Bacterial infections usually produce progressive CSF changes, whereas viral infections produce no significant changes in CSF in this short period.

Neonatal Infections

Herpes simplex virus infections.—HSV may produce severe, rapidly progressive neonatal infections. The virus is transmitted to the

infant in several ways. Intrauterine infection may occur secondary to maternal viremia. The usual method of acquiring infection is by passage of the infant through the infected birth canal, the usual site of maternal infection being chronic cervicitis. A third method of acquiring infection is through exposure to persons with active herpetic infections such as herpes labialis, gingivostomatitis or recurrent infections of the skin.

Neonatal infections acquired secondary to maternal viremia may be caused by HSV, type 1 (HSV-1) or HSV, type 2 (HSV-2). Infections acquired in passage through the birth canal are caused by HSV-2, and those from environmental sources may be either type.

Transplacental infection early in pregnancy may result in fetal wastage or anomalies. Intrauterine infection during the latter part of pregnancy results in the clinical picture of neonatal sepsis, which is comparable to that caused by other etiologic agents such as bacteria, CMV, *Toxoplasma gondii* or rubella virus. The infants usually are small for gestational age, and present with jaundice, hepatosplenomegaly, seizures, lethargy, poor feeding and vesicular skin lesions, often in a zosteriform distribution (Fig. 8). Infections acquired at birth may not become clinically manifest until several days later. The initial symptoms, such as poor feeding, temperature instability and lethargy, are followed by rapid development of the full-blown clinical picture of sepsis, with or without encephalitis. The finding of even a single vesicle, from which virus is easily recovered, is very suggestive of disseminated herpetic infection. Rapid deterioration of the patient's condition is characteristic, and complications such as disseminated intravascular coagulation, circulatory and respiratory collapse and destruction of the brain are frequent. In patients with encephalitis the CSF is abnormal, with increased leukocytes and elevated protein content. Protein content of the CSF usually continues to rise.

Infants are peculiarly susceptible to herpes infections, and most infections result either in death or severe neurologic sequelae in those who survive.

There is no satisfactory treatment for disseminated neonatal herpetic infections. Meticulous supportive care and treatment of complications are necessary. Treatment with adenine arabinoside is under study, but as yet no information is available.

The most effective method of dealing with neonatal herpetic infections is to prevent them. Active herpes infection of the birth canal at term is an indication for cesarean section. It is also important to avoid exposure of the neonate to HSV both in the home and in the hospital environment.

Neonatal herpetic infections are diagnosed only if suspected. One of the earliest clues to diagnosis is the appearance of one or more vesicular skin lesions; and, when found, the lesion should be cultured; if chemotherapy is to be used, it should be started while awaiting con-

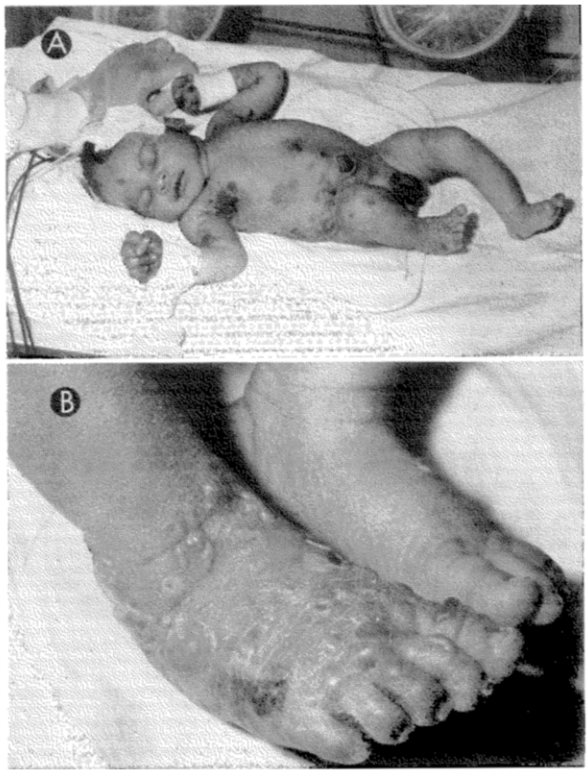


FIG. 8.—*A*, patient with disseminated neonatal herpes. Note somewhat zosteriform distribution of the vesicular rash. *B*, same patient showing vesiculobullous lesions of the feet.

firmation by recovery of virus from the lesion. There are reports of disseminated neonatal herpetic infections followed by a favorable outcome in the absence of chemotherapy, but, in general, disseminated neonatal infections with or without encephalitis carry a grave prognosis.

CYTOMEGALOVIRUS INFECTIONS

The human CMV is a ubiquitous agent, with a DNA core and icosahedral capsid measuring 2,000 Å. Like other members of herpesviruses, the CMV commonly produces latent and/or chronic infections. Cytomegalic inclusion disease is seen in infancy as a result of intrauterine infection. In adults and older children CMV infections appear to be latent and become apparent in patients with impaired host responses. CMV infections have been recognized with increasing frequency in patients with neoplasms who are immunosuppressed or in recipients of organ transplants. In these patients the virus frequently

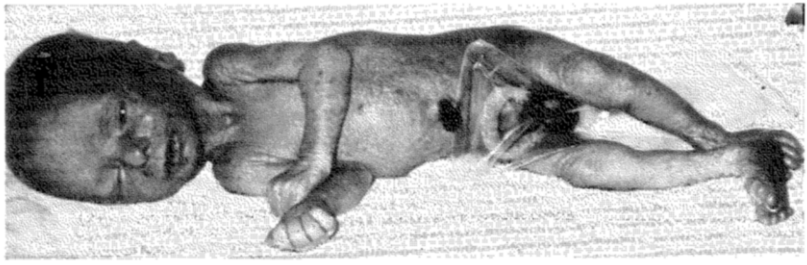
causes acute pneumonia or hepatitis. CMV mononucleosis is characterized by malaise, myalgia, fever, lymphocytosis, abnormal liver functions and serologic tests that are negative for infectious mononucleosis. This syndrome has been described in patients after transfusion and after heart surgery as well as in previously healthy individuals. The virus has been isolated from the urine of these patients.

In congenitally acquired infections, the virus is transmitted transplacentally from the mother with a primary CMV infection to the fetus. The transmission occurs regardless of the stage of pregnancy. Large scale studies have shown the incidence of neonatal infection to be about 1%. Maternal infection during the first trimester is associated with multiple organ involvement, including CNS, with microcephaly and cerebral calcifications. Although the mother may excrete the virus for indefinite periods of time, subsequent pregnancies usually are unaffected. This protection apparently is due to the maternal antibodies acquired during the initial infection.

The clinical features of neonatal CMV infection vary from frank involvement of multiple organs, with intrauterine growth retardation, hepatosplenomegaly, jaundice, hepatitis, petechiae, thrombocytopenia, microcephaly, cerebral calcification and chorioretinitis, to minimal abnormalities such as transient thrombocytopenia and to complete lack of symptoms but excretion of the virus (Fig. 9). Infants with CMV disease excrete the virus in their urine for a period of months to several years. This protracted period of viral shedding serves as a source for dissemination.

DIAGNOSIS.—The most sensitive method for diagnosis of CMV infection is isolation of the virus from the patient's urine. The virus can be isolated from throat, blood and tissue specimens. Virus is cultured in human fibroblasts, causing focal lesions followed by appearance of large intranuclear eosinophilic inclusion bodies. Detection of these inclusion bodies in the epithelial cells of the urinary sediment also represents a valuable diagnostic test.

FIG. 9.—Typical appearance of an infant with severe congenital infection such as rubella or cytomegalic inclusion disease. The head is of normal size. Note the relatively small body, wrinkled skin indicative of the absence of subcutaneous fat and "blueberry muffin" lesions secondary to bleeding into the skin.



Detection of specific CMV immunoglobulin M (IgM) antibody by indirect immunofluorescence is a helpful diagnostic aid in symptomatic patients, but this test often is negative in asymptomatic infants who excrete the virus.

TREATMENT.—Although antiviral agents such as adenine arabinoside have been proposed for treatment of this infection, the efficacy is unproved. No method of prevention is available.

CONGENITAL RUBELLA

Rubella occurring during the first trimester of pregnancy is associated with a high incidence of congenital anomalies, as well as fetal wastage. The risk of maternal rubella causing anomalies is greatest during the first 4 weeks of pregnancy and then decreases during the next 8 weeks.

Infants with congenital rubella are remarkably similar to those with either congenital disseminated neonatal herpes or cytomegalic inclusion diseases. The infants are small for gestational age, with markedly decreased subcutaneous fat, hepatosplenomegaly, jaundice, altered sensorium, neurologic abnormalities and impaired coagulation. Bleeding into the skin produces the characteristic "blueberry muffin" lesions (see Fig. 9). In addition to this picture of neonatal sepsis, with encephalitis, other stigmata of the rubella syndrome help to differentiate these infants from those with other severe congenital infections. The most common defects are congenital heart lesions such as patent ductus arteriosus or endocardial cushion defects, cataracts and microcephaly. Other defects such as sensorineural deafness and congenital cataracts may not be recognized until later.

Laboratory studies reveal increased bilirubin, primarily of the indirect reacting fraction, thrombocytopenia and abnormalities of the CSF, including increased leukocytes and elevated protein content. The IgM levels are elevated, and demonstration of significant levels of antibodies against rubella in this fraction is diagnostic. Specific diagnosis can be made by recovery of the virus from the infant. Antibody studies are not diagnostic since maternal antibodies do cross the placenta.

INFECTIOUS MONONUCLEOSIS

ETIOLOGY.—E-B virus has been implicated as the cause of infectious mononucleosis, although it has neither been isolated from patients with the disease nor grown in cell cultures. In patients recovering from mononucleosis, antibodies develop that react with viral particles found in cell lines derived from Burkitt's lymphoma. Several studies have documented the protective effect of these E-B viral antibodies against development of disease. E-B virus has been demonstrated by electron microscopy and immunofluorescence in cultures of blood leukocytes taken from patients during and after recovery from mono-

nucleosis. A transforming factor has been isolated from throat secretions of patients with infectious mononucleosis. This factor is capable of transforming cord blood leukocytes into continuous cell lines. Its activity can be neutralized by specific E-B antibody and can be detected as late as 16 months after onset of symptoms. Induction of disease by E-B virus inoculation into a susceptible host has been indirectly reported, but such studies should be approached with concern about untoward results. Koch's postulates remain unfulfilled, but the relationship between infectious mononucleosis and E-B virus has been clearly demonstrated.

CLINICAL PICTURE.—Forty years ago Tidy described three clinical presentations of mononucleosis: (1) a glandular form characterized by a short prodromal period followed by enlargement of any or all groups of lymph nodes, with or without accompanying constitutional symptoms; (2) an anginose form of pharyngitis, with injection or membrane formation; and (3) a febrile form seen in adults, with malaise, fever, headache and frequent chills. Lymph node enlargement may occur at any time during the illness in the third form. The classic triad of fever, exudative pharyngitis and adenopathy may be present in only 40–50% of patients. The early symptoms are nonspecific, most patients experiencing malaise, low grade fever, headache and sore throat. Fever ranges from 99°–104° F and subsides by 21–28 days in the majority of patients. Relapse after 5 or more days without fever is rare. Posterior cervical lymph node enlargement differentiates mononucleosis from other causes of cervical adenopathy. The nodes are bilateral, discrete, usually nontender, nonsuppurative and they may produce a "bull-neck" appearance. Axillary and inguinal adenopathy may be present. By the end of the first week the throat becomes diffusely injected or has a membranous exudate over the tonsils. A palatal enanthem, consisting of crops of sharply circumscribed petechiae of the uvula or the soft palate just about the uvula, appears between the 5th and 12th days. Secondary infection with fusobacteria and hemolytic streptococci gives the breath a foul odor. Severe hyperplasia of the nasopharyngeal lymphoid tissue causes nasal obstruction with secretions and gives a nasal quality to the voice; it may lead to refusal to swallow water or even saliva (Fig. 10). Rarely, severe lymphoid hyperplasia may produce tracheal compression requiring tracheostomy. The face is frequently puffy, with edema of the eyelids. Hepatosplenomegaly is common, and splenomegaly may persist for months.

A skin rash, usually maculopapular but sometimes petechial, vesicular, urticarial, morbilliform or scarlatiniform, occurs in 3–15% of patients. Young children, under 3 years of age, seem to have symptoms other than those described above, often presenting with gastroenteritis, bronchopneumonia or hepatosplenomegaly. Heterophil titers often are negative, and the diagnosis can be made only by detection of specific antibody to E-B virus.

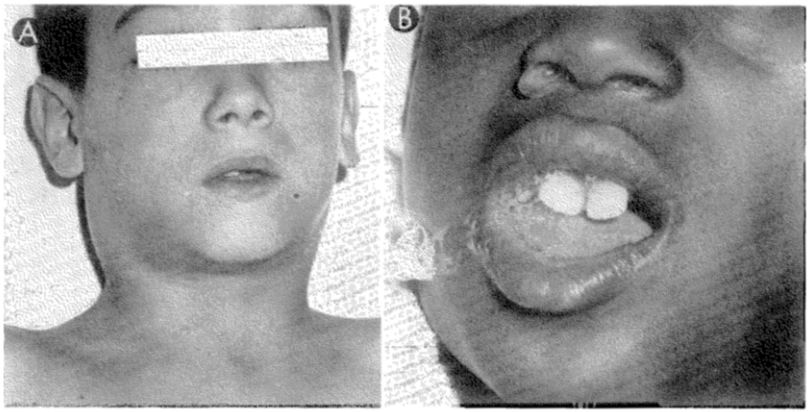


FIG. 10.—*A*, typical appearance of the neck caused by lymphadenopathy in infectious mononucleosis. *B*, patient with infectious mononucleosis with severe nasal obstruction. Drooling was caused by refusal to swallow. The patient was treated with steroids because of increasing respiratory distress secondary to marked tonsillar and adenoidal hypertrophy.

Infectious mononucleosis may present with unusual manifestations such as hepatitis, urticaria, hemolytic anemia, purpura, palmar dermatitis, carditis, arthritis and various neurologic abnormalities. Such unusual presentations may delay the correct diagnosis. These manifestations usually resolve completely during the course of the disease, though they may rarely lead to serious complications or result in a fatal outcome.

COMPLICATIONS.—Hepatic dysfunction occurs in over 80% of patients and perhaps should be considered as part of the spectrum of disease rather than as a complication. Abnormalities of liver function usually are transient; however, fatal hepatic necrosis associated with infectious mononucleosis has been reported.

CNS involvement occurs in 0.7–5% of patients and may cause death. Neurologic abnormalities include meningoencephalitis, polyradiculopathy, transverse myelitis, Guillain-Barré syndrome, unilateral facial palsy, ophthalmic defects or an expanding occipital mass.

Two life-threatening complications secondary to severe lymphoid tissue hyperplasia are acute airway obstruction, requiring intubation or tracheostomy, and splenic rupture. The spleen is tense and swollen, with thinning of the splenic capsule and trabeculae. There is normal and abnormal lymphocytic infiltration around the intratubular arteries, intima of veins and blood sinuses.

Other more common but benign complications include the maculopapular, pruritic rash that occurs in as many as 95% of patients with mononucleosis who are given ampicillin. Rash also occurs in a significant number of patients given penicillin (43%), complicating the

treatment of the 30% or more who have an associated streptococcal pharyngitis.

Other unusual complications include hemolytic-uremic syndrome, orchitis, pneumonitis, mediastinal mass, Reye's syndrome, electrocardiographic abnormalities and protein-losing enteropathy. The multiorgan involvement of infectious mononucleosis was demonstrated in autopsy material from a patient who died traumatically after recovering from the disease 2–3 weeks earlier. Monocellular infiltrates were found in liver, kidney, heart, lungs, brain, adrenals and testes.

The over-all mortality rate in infectious mononucleosis is probably less than 1 per 3,000 cases.

DIAGNOSIS.—Diagnosis is based on clinical manifestations and laboratory tests. Peripheral blood count reveals lymphocytosis of at least 50%, and 10% of these cells are so-called Downey cells or atypical lymphocytes. These cells are larger than normal lymphocytes and have abnormally shaped nuclei, dense chromatin network and vacuolated, foamy cytoplasm. The total leukocyte count is normal or low during the first week, increasing to 10,000–20,000 cells per cu mm during the second week. Hepatic dysfunction, with elevation of serum glutamic oxaloacetate transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT) and lactic acid dehydrogenase (LDH) also should be considered a diagnostic criterion.

HETEROPHIL AGGLUTINATION TEST.—Paul and Bunnell in 1932 demonstrated high titers of agglutinins against sheep erythrocytes in the sera of patients with infectious mononucleosis. Heterophil antibodies, in low titer, also are found in patients with serum sickness and in normal persons (Forssman antibodies). Therefore, a differential adsorption test was introduced by Davidsohn in 1937.

HETEROPHIL AGGLUTINATION WITH DIFFERENTIAL ADSORPTION TEST.—This test is based on the observation that heterophil agglutinins produced during infectious mononucleosis are adsorbed by beef erythrocytes but not by guinea pig kidney cells. The reverse is true for the Forssman-type, normally occurring, heterophil agglutinins. In serum sickness, antibodies are removed both by the guinea pig kidney cells and by the beef erythrocytes. A fourfold difference between the guinea pig kidney and the beef erythrocyte titers is considered significant in diagnosing infectious mononucleosis. These adsorption patterns are presented in Table 4. Heterophil antibodies usually appear by the end of the first week and, although they may disappear by the end of the second week, they may persist for 4 weeks or longer. Consequently, if negative, this test should be repeated long enough after onset of the illness to permit serologic conversion.

SPOT TESTS.—In recent years several slide tests have been developed. The Monospot is among the most widely used. It is a differential test in which adsorption with guinea pig kidney and beef erythrocytes is performed on a slide. Horse erythrocytes, instead of sheep red cells,

TABLE 4.—ANTIBODY ADSORPTION PATTERNS

ANTIBODY TYPE	GUINEA PIG KIDNEY CELLS	BEEF ERYTHROCYTES
Forssman	Yes	No
Infectious mononucleosis	No	Yes
Serum sickness	Yes	Yes

are used as the reactor cells. One drop of each reagent is mixed with the patient's serum on a slide. One drop of the reactor cells (horse erythrocytes) is then added and allowed to agglutinate for 1 minute. The test is positive if a stronger and earlier agglutination is seen after adsorption with guinea pig kidney cells than after adsorption with beef erythrocytes.

The Monospot is reliable and rapid and requires only a small amount of capillary blood from the patient. False negative results are extremely rare. False positive reactions are infrequent (5–14%) and usually are transient, but have been reported occasionally in rubella, viral hepatitis, CMV infection, leukemia, adenovirus infection and pancreatic carcinoma (two instances). In most patients the slide test can be a reliable substitute for the heterophil antibody test.

E-B VIRUS-SPECIFIC SERODIAGNOSTIC TEST.—These tests are preferable to nonspecific tests. They are indicated in younger children who may present with an unusual clinical picture, or in patients with persistently negative heterophil antibody titers (10% of the adult population and a higher percentage of children) in whom the diagnosis is suspected on a clinical basis.

Antibodies to E-B virus in the sera of patients with infectious mononucleosis were described by Henle *et al.* in 1974. These antibodies were the same as those found in the sera of children with Burkitt's lymphoma. It soon became evident that E-B virus antibodies could be found in many other clinical conditions, such as Hodgkin's lymphoma and nasopharyngeal carcinoma, as well as in 10–90% of the normal population. The latter percentage varies according to the age and socioeconomic status of the population studied.

In recent years several technics that measure antibodies to different antigens of the E-B virus have been developed. E-B virus-specific IgM antibodies appear during the incubation period, rise to a high titer during the acute phase and cannot be detected during convalescence. This test detects primary infection and therefore is very helpful in diagnosing current infectious mononucleosis. For general use, the "triple layer" immunofluorescent technic of Schmitz *et al.* is the most promising. This test can be done easily and rapidly.

Antibodies to the diffuse component of the early antigen are detected in the acute phase serum of 70–80% of patients with infectious mononucleosis. Titers decline and disappear during the convalescent

phase. These IgG antibodies are measured by indirect immunofluorescent technic (Henle *et al.*).

Antibodies to the E-B virus capsid antigen can be measured using indirect immunofluorescent technic. Historically, these antibodies were the first to be detected in infectious mononucleosis (Henle *et al.*). Titers begin to rise during the early acute phase and decline later but remain detectable for several years, probably for life. This is the most widely used test for epidemiologic surveys of infectious mononucleosis.

Neutralizing antibody (Hewets *et al.*) titers also rise during the acute phase and persist for many years. This test is complicated and performed by few laboratories.

Complement fixing antibodies to soluble antigen (Vonka *et al.*) and antibodies to E-B virus-associated nuclear antigen appear during the convalescent phase and remain elevated for several years. These tests are useful for determining immunity to infectious mononucleosis but are not yet performed routinely.

THERAPY.—Therapy in most cases of infectious mononucleosis is supportive. Analgesics for relief of pain and saline washings for sore throat are helpful.

Pharyngitis caused by group A *Streptococcus pyogenes* occurs frequently with infectious mononucleosis. Therefore, if the patient is unusually toxic, a throat culture should be done and, if positive, appropriate antibiotic therapy is indicated.

The use of steroids in the treatment of infectious mononucleosis is controversial. Bolden *et al.* in a double-blind study have shown that a 12-day course of prednisone hastens the return of a normal temperature, differential leukocyte count and heterophil antibody titers. We believe that steroids should be reserved for serious complications such as upper airway obstruction, CNS involvement and hematologic abnormalities (e.g., thrombocytopenia and hemolytic anemia). In upper airway obstruction, improvement can occur so promptly that endotracheal intubation or tracheostomy is avoided. We recommend prednisone in full dose (60 mg/m^2/day) until airway obstruction is relieved. Dosage then may be rapidly tapered and discontinued.

ACUTE VIRAL HEPATITIS

Acute viral hepatitis is a systemic infectious disease that affects the liver predominantly. The term includes two clinically similar forms: hepatitis A and hepatitis B. The previously used names, infectious hepatitis and serum hepatitis, are no longer accurate because both forms of the disease can be transmitted by either the oral or the parenteral route. Synonyms for hepatitis A include infectious hepatitis, short incubation hepatitis, MS-1 hepatitis and catarrhal hepatitis. Hepatitis B also has been known as serum hepatitis, long-incubation hepatitis, Australia antigen hepatitis and MS-2 hepatitis.

Studies in human volunteers have shown that at least two viruses,

hepatitis virus A and B, cause viral hepatitis. Although attempts to culture hepatitis A and B viruses in tissue or to transmit them to animals have failed, they exhibit several viral characteristics. They pass through bacteria-retaining filters, resist freezing for a long period of time and are not destroyed by heating at 56° C for 30 minutes. They also are resistant to chlorine and ether.

HEPATITIS B ANTIGEN.—In 1963 Blumberg and associates discovered an antigen in the serum of an Australian aborigine that reacted with sera from multiply transfused hemophilic patients. This antigen was originally called Australia (Au) antigen. Subsequent studies identified this antigen in the sera of patients ill with hepatitis B, but not with hepatitis A. Hence, alternative designations of Au antigen included hepatitis-associated antigen, serum hepatitis antigen and the currently preferred hepatitis B surface antigen (HB_sAg).

Three different particles have been identified by electron microscopy in liver specimens taken from patients with acute hepatitis. The Dane particle is 42 nm in diameter, the long tubular form 20 nm in diameter and the small sphere 20 nm in diameter. The Dane particle may turn out to be the hepatitis B virus. This particle consists of a core and an outer surface component, each having specific antigenic properties. The surface component is antigenically similar to the 20 nm particles. Thus, according to the current nomenclature HB_sAg is the hepatitis B antigen found on the *surface* of the Dane particle and on the unattached 20 nm particles. The hepatitis B antigen found within the *core* of the Dane particle is denoted HB_cAg.

HB_sAg is found in the sera of more than 90% of patients who have hepatitis B. It also has been demonstrated in the nuclei and cytoplasm of the liver cells of some patients with hepatitis B. The antigen usually is detectable in the serum 2 weeks to 2 months before evidence of abnormal SGOT activity. The duration of HB_sAg in the blood is variable: it usually disappears within several weeks or months, but occasionally it persists for years. Chronic carriers of HB_sAg may be completely asymptomatic and have normal or abnormal liver function tests. Mothers with acute hepatitis B seem to be more infectious in transmitting HB_sAg to their babies than mothers who are asymptomatic chronic carriers. In both cases, however, persistent antigenemia and abnormal liver function tests have been found in some babies. Epidemiologic studies suggest that the tendency for the persistence of HB_sAg is inherited as an autosomal recessive genetic factor. HB_sAg was found in the sera of 0.1% of the normal population of Europe and the United States. A higher incidence (3–25%) of HB_sAg was demonstrated in the sera of residents of tropical countries; patients with Down's syndrome, Hodgkin's disease, lepromatous leprosy and leukemia; needle-using drug addicts and patients being treated with chronic hemodialysis.

EPIDEMIOLOGY.—Hepatitis A is more common in children and in

young adults; hepatitis B shows no age preference. Both hepatitis A and B are of worldwide distribution. The common mode of transmission of hepatitis A is the fecal-oral route, primarily person-to-person contact. Common-source outbreaks due to contaminated water, milk or uncooked seafood have been associated with hepatitis A. Hepatitis B most often is transmitted parenterally, although it may be spread by the fecal-oral route. Outbreaks of hepatitis B are not as common as hepatitis A except in patients and personnel at hemodialysis centers and among parenteral drug abusers. Transfusion of whole blood, serum and plasma or the use of infected needles, syringes and tattooing instruments may be the source of hepatitis B, as well as of hepatitis A. The risk of clinically apparent hepatitis following transfusion is between 0.5 and 13 cases per 100 transfused patients. The risk of anicteric hepatitis following transfusion may be 3–20 times greater. Exposure to asymptomatic carriers of HB_sAg or to persons with undiagnosed anicteric hepatitis also represents a significant source of infection.

PATHOLOGY.—The pathologic changes of acute viral hepatitis A and B are indistinguishable by light microscopy. Both cause swelling and necrosis of the liver cells, with mononuclear cell infiltration of the portal zones. Studies with electron microscopy have shown intranuclear and cytoplasmic virus-like particles in some patients with HB_sAg-positive hepatitis.

Viral hepatitis can also lead to massive necrosis of the liver (acute yellow atrophy). The liver cells are completely destroyed and there is no evidence of their regeneration.

CLINICAL MANIFESTATIONS.—The severity varies from an asymptomatic carrier state of HB_sAg to fulminant hepatic necrosis and death. In most instances hepatitis is a self-limiting disease in which the case fatality rate is low, and recovery is the rule. In children the anicteric form is more common, and the disease is generally less severe than in adults. The ratio of icteric to anicteric hepatitis A is estimated to be 1:10 in children and 1:1 in adults. Virus B usually causes a more severe hepatitis than does virus A.

The incubation period is 15–40 days for hepatitis A and 50–180 days for hepatitis B. Virus is found in the blood 2–3 weeks before the onset of jaundice in hepatitis A, and HB_sAg may be found as early as 3 months prior to the onset of jaundice in hepatitis B. Hepatitis virus A is excreted in the feces during the last 2 weeks of illness. Although oral transmission occurs in hepatitis B, the period when the virus is excreted from the feces is not known.

Preicteric phase.—Two to 14 days days before the onset of jaundice, symptoms of malaise and fatigue develop. Anorexia and a particular distaste for coffee and cigarettes occur. The patient may complain of epigastric or right upper quadrant pain. Onset with fever (100–104° F) and flu-like symptoms (coryza, cough, myalgia) are

more common with hepatitis A and usually begin abruptly. Hepatitis B has a more insidious onset, and high fever is uncommon. Dark-colored urine and light-colored feces are noted 1–4 days before the onset of jaundice.

A serum sickness-like picture, with urticaria, skin rashes and polyarthritis is seen in 0.4–25% of patients with hepatitis B and less frequently with hepatitis A. These symptoms may be due to an immunocomplex disease caused by HB_sAg.

Icteric phase.—The prodromal symptoms of fever and gastrointestinal discomfort subside after jaundice appears. Appetite usually returns, and the patient is asymptomatic when jaundice is most severe. Pruritus is common in adults but rare in children. The liver usually is palpable and tender. Splenomegaly and posterior cervical lymphadenopathy are found in about 20% of patients. The icteric phase has an average duration of 8–11 days in children and up to 3–4 weeks in adults.

Convalescent phase.—Convalescence usually is rapid and uneventful in children. In adults fatigue may be prominent and lasts for several weeks or longer.

LABORATORY FINDINGS.—The presence of HB_sAg in hepatitis B is the only laboratory distinction from hepatitis A. In the preicteric phase there is usually leukopenia. Toward the end of this phase atypical lymphocytes, 2–20%, appear. A sustained leukocytosis is evidence against viral hepatitis. During the prodromal phase there is progressive elevation of SGOT and SGPT levels, SGPT usually being higher than SGOT. Peak SGPT levels between 400 and 3,000 units are characteristic. Transaminase levels may return to normal in 2–3 weeks but sometimes persist for several months. When clinical jaundice is detected, serum bilirubin usually is about 3 mg% and may reach 5–20 mg%. Serum alkaline phosphatase is slightly elevated (5–15 Bodansky units). Thymol turbidity increases several days after SGOT and returns to normal later. Elevation of IgG and IgM may occur during the acute phase.

SEROLOGIC FINDINGS.—Antibody to HB_sAg, anti-HB_s, was found in 20% of the population tested in the Washington, D. C., area. The male/female ratio was equal. Unexplained was the high frequency (19%) of anti-HB_s in the 2–4-year-old group and the absence of antibody in the 15–19-year age group. Anti-HB_s was of both the IgG and IgM class, neither consistently being detected early nor showing a definite pattern of transmission or persistence. Anti-HB_s was found in 83% of multiply transfused patients and in 23% of commercial blood donors. It has not been detected in patients infected with hepatitis A.

In some patients anti-HB_s develops prior to the appearance of clinical hepatitis or of HB_sAg. This may be an anamnestic response to previous subclinical exposure to HB_sAg. Although there may be a correlation between early antibody response and resistance to overt illness

after exposure, antibody to HB_sAg may not imply immunity. Reinfection may be due to a different subtype of virus, or anti-HB_s may not neutralize the infectious virion core.

DNA polymerase, associated with the core of the Dane particle, correlates with the period of peak hepatitis B virus replication. Antibody to the core antigen, anti-HB_c, has been detected in sera of blood donors implicated in cases of posttransfusion reactions who had no detectable HB_sAg or anti-HB_s. Anti-HB_c also was found in 1% of 200 HB_sAg-negative blood donors, in 98% of 363 HB_sAg-positive blood donors and in 100% of 100 chronic HB_sAg carriers. It may be the most sensitive indicator of viral replication. Assaying for HB_sAg, anti-HB_s, anti-HB_c and DNA polymerase may give the most complete information in screening blood products and in diagnosing hepatitis B.

IMMUNIZATION.—Immune serum globulin given prior to or early after exposure to viral hepatitis A can prevent clinical manifestations of disease, although enzymatic changes still occur. Immune globulin with high titers of anti-HB_s appears to protect against viral hepatitis type B transmitted nonparenterally.

Early studies failed to show the efficacy of immune serum globulin pre- or postoperatively to prevent posttransfusion hepatitis. Katz has shown a decrease in posttransfusion hepatitis when modified gamma globulin was added to blood prior to transfusion.

Krugman has used heat-inactivated sera containing the prototype hepatitis B virus, MS-2 strain, to actively immunize children against a challenge of the same virus in its infectious form. He demonstrated that prior immunization leads to attenuated infection; a decrease in the chronic carrier state of HB_sAg; and a blocking of the appearance of HB_sAg, DNA polymerase and anti-HB_c. This work may lead to the development of an attenuated viral vaccine.

TREATMENT.—No specific treatment for infectious hepatitis is required. Bed rest is necessary only through the acute stages of the disease: previously healthy military recruits had no prolonged ill effects or increase in relapse rate after embarking on an early exercise program following infectious hepatitis. A balanced diet should be offered when the patient's appetite returns. Corticosteroid therapy is not indicated in uncomplicated cases and may lead to increased relapse rates, chronic disease or other complications (peptic ulcer, pyogenic infection). Fulminant hepatitis with liver failure may complicate the course, and appropriate therapy should be carried out, including protein restriction, sterilization of the gut and provision of adequate calories as carbohydrates.

ROLE OF THE VIRUS DIAGNOSTIC LABORATORY

After it has been established that there is a cause and effect relationship between certain viruses and certain diseases, the ideal method for

making an etiologic diagnosis is to recover the virus from the site of pathology. The recovery of a virus, with concomitant serologic conversion, from a source other than the site of pathology is proof of infection, but not necessarily proof that the virus is related to the disease in question. In addition, serologic studies are expensive and time consuming.

Herrmann has very clearly and correctly stated the case for the practicality and feasibility of specific viral diagnosis, and he has clearly documented the problems and the impracticality of the diagnostic approach of the classic virologist. In a word, serologic studies are at best presumptive and of necessity retrospective and therefore of little or no value in the management of the patient.

The use of several different cell cultures permits the recovery of most viruses that cause infections in children with sufficient frequency and rapidity to affect patient care. If one takes into account the source of the specimen, suspected diagnosis, age of the patient, season, time required to produce cytopathology and cytopathologic changes produced in cell culture, the virus can be recognized with a high degree of accuracy. The specific serotype of an enterovirus isolated from a specimen of CSF is generally of no importance. On the other hand, the recovery of an enterovirus from CSF often can be reported in as little as 24 hours and usually within 72 hours. This information is extremely helpful in the care of the patient.

CONCLUSION

Even though epidemiologic studies show that most infections in children are caused by viruses, antibiotics are used to treat many of these patients. Antibiotics are of no value in the treatment of viral infections, nor is there evidence to suggest that antibiotics prescribed for viral infections decrease the incidence of secondary bacterial infections.

The promiscuous use of antibiotics adds to the already burdensome cost of medical care and may cause untoward reactions ranging from mild gastrointestinal disturbances to severe toxic manifestations such as deafness, renal and hepatocellular damage, bone marrow suppression, fatal aplastic anemia and fatal anaphylaxis. Antibiotics also produce marked changes in the normal flora and predispose the patient to the development of secondary infections, which are invariably difficult to treat.

The practicing physician often finds himself on the horns of a dilemma. The lay public expects, indeed often demands, antibiotics for almost any illness, infectious or not. The physician often hesitates to withhold antibiotics in the face of a possible bacterial infection, or he may believe erroneously that if antibiotics do no good, they will surely do no harm. He may also think that specific etiologic diagnosis is un-

necessary if one or more antibiotics are prescribed to provide broad coverage of the probable etiologic agents.

Except in life-threatening infections, the use of antibiotics can often be avoided by careful evaluation of the patient over a period of several hours, along with selected laboratory studies. In most cases bacterial infections are progressive and are associated with increasing toxicity. On the other hand, viral infections tend to reach a plateau and for a period of several days there is neither progression nor improvement.

Our experience suggests that if we assume the attitude that antibiotics will not be prescribed without reasonable indication, such as life-threatening infections or strong evidence of bacterial etiology, antibiotic usage can be greatly reduced without significant threat to the patient. It is a goal for which practicing physicians should strive.

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