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Pediatr. Rev. 1985;7;35-44

DOI: 10.1542/pir.7-2-35

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The Many Faces of Infectious Mononucleosis: The Spectrum of Epstein-Barr Virus Infection in Children

Charles Grose, MD*

Infectious mononucleosis is a disease well known to every pediatrician. Who has not seen the previously robust teenager who slowly becomes less active, develops low-grade fever and a sore throat, and complains of being tired all the time? Upon arriving at the physician's office with these complaints the teenager is usually given a "Mono-Spot" test (almost routinely). The test results are often strongly positive. The pediatrician then must discuss the diagnosis with both the teenager and the parents and must respond to the attendant questions. Is the disease really acquired by kissing? How serious is it? Are there any lasting effects? Will the feeling of tiredness ever go away? Is infectious mononucleosis a form of cancer? Can I have the disease more than once? Is there any therapy? The answers to many of the above questions have changed dramatically over the last 5 to 10 years. The spectrum of infectious mononucleosis continues to be expanded and now includes acute, subacute, and chronic disease states, each with its own separate set of problems. Subclinical disease can now be diagnosed in younger children with an obscure febrile illness. On rare occasions, overwhelming infectious mononucleosis results in death in some young children, especially boys. This review, therefore, will emphasize the expanded spectrum of illnesses associated with infectious mononucleosis. The review will begin with a brief discussion of the etiologic agent and probable pathogenetic mechanism. In the concluding sections, potential therapeutic approaches will be elaborated.

PAUL-BUNNELL TEST AND RAPID SLIDE AGGLUTINATION TESTS

A landmark in the diagnosis of in-

fectious mononucleosis was a fortuitous observation by Paul and Bunnell in 1932. They observed that the sera from most patients with infectious mononucleosis agglutinated sheep red blood cells. They did not know the source of the antibody, which was discovered during the analysis of sera from patients with serum sickness. Davidsohn, in 1938, discovered that heterophil agglutinins of infectious mononucleosis could be differentiated from those of other diseases, including serum sickness, by a series of adsorption techniques. When the serum from a patient with infectious mononucleosis was incubated with bovine erythrocytes, the heterophil agglutinins were removed. In contrast, the heterophil antibody titer of the same serum was unaffected by adsorption with guinea pig tissue.

As a substitute for the traditional Paul-Bunnell-Davidsohn test, most hospital laboratories today use one of the commercially available rapid slide tests to detect heterophil antibody. Some commercially available rapid slide heterophil antibody kits are: Mono-Sure (Wampole Lab, Cranbury, NJ), Diagluto-IM (Beckman Lab, Fullerton, CA), Mono-Spot (Ortho Diagnostics, Raritan, NJ), and Monosticon (Organon Diagnostic, West Orange, NJ). The rapid slide test is sensitive, specific, and simple to perform. Because hemagglutination activity in serum is even higher against horse erythrocytes than against sheep red blood cells, many of the rapid slide tests use a horse cell substrate. The sensitivity of the rapid slide test is comparable to that of the traditional Paul-Bunnell-Davidsohn test, with the possible exception of testing sera collected from children less than 4 years of age (Fig 1). In the very young, the modified Paul-Bunnell-Davidsohn test with horse red blood cell substrate appeared to be the most sensitive assay for detection of heterophil antibody responses. Nevertheless, the rapid slide agglutination test is an extremely useful screening pro-

EDUCATIONAL OBJECTIVE

12. The pediatrician should be able to do a systematic evaluation of a child with prolonged fever, and be able to differentiate among systemic juvenile rheumatoid arthritis, infectious mononucleosis, leukemia, leptospirosis, subacute bacterial endocarditis, serum sickness, other viral infection, drug fever or atypical measles, and to be able to manage each appropriately (Topics, 85/86).

cedure that can be performed quickly within either a hospital or office laboratory. For consistency of results over time, it is preferable to use a product from only one commercial supplier.

EPSTEIN-BARR VIRUS

The etiologic agent of infectious mononucleosis is the Epstein-Barr virus (EB virus), a member of the family of human herpesviruses; other members include herpes simplex viruses 1 and 2, varicella-zoster virus, and cytomegalovirus. The association of infectious mononucleosis with Epstein-Barr virus infection is a relatively recent discovery. In 1958, Burkitt, a British surgeon, first described a peculiar lumpy tumor of the jaw which occurred in young children living in certain regions of equatorial East Africa. Herpes-like viral particles subsequently were demonstrated within cell cultures established from the tumors, and the virus was designated Epstein-Barr (EB) virus after two of the original British researchers. In 1968, Werner Henle and Gertrude Henle (Philadelphia) discovered that patients with acute infectious mononucleosis lacked antibody to EB virus prior to having the disease and developed antibody to EB virus within weeks after onset of symptoms. These results were quickly confirmed

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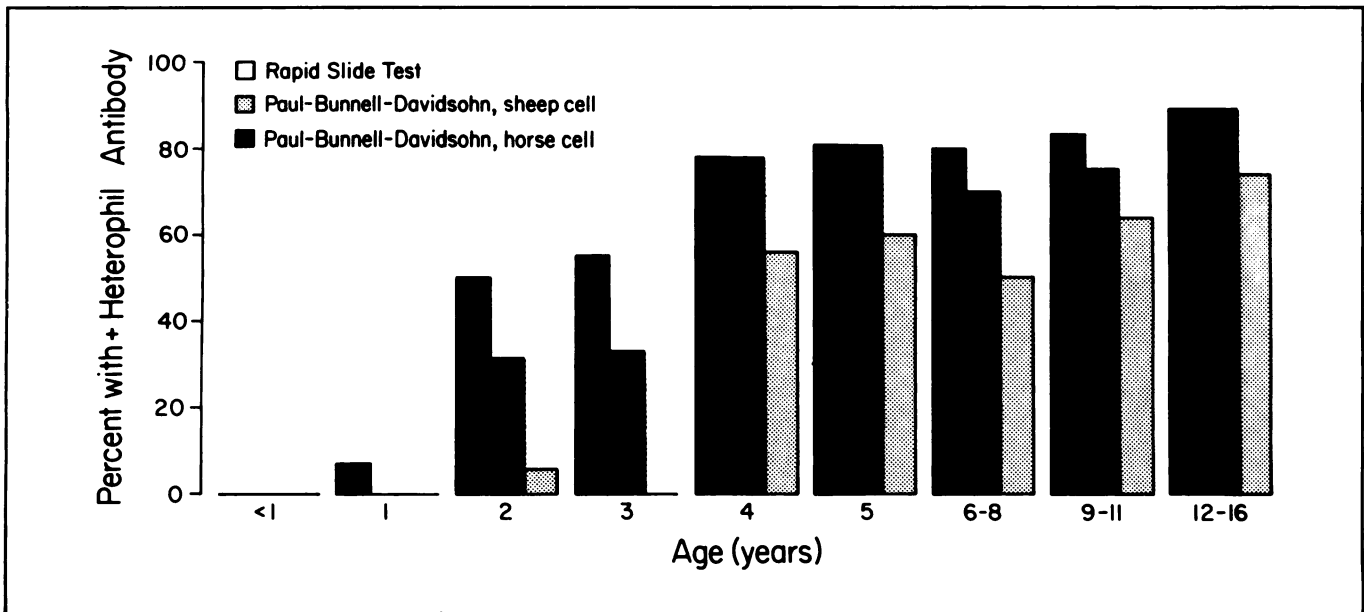


Fig 1. Comparison of heterophil antibody responses in children with infectious mononucleosis. Serum samples were collected from children with infectious mononucleosis who ranged in age between 1 and 16 years. Sera were tested for heterophil antibody by three different assays: rapid slide agglutination test (Wampole Laboratories), Paul-Bunnell-Davidsohn test with sheep cell substrate, and Paul-Bunnell-Davidsohn test with horse cell substrate. (Reprinted with permission from Schlossberg D (ed): *Infectious Mononucleosis*, New York, Praeger Publishers, 1983, p 115.)

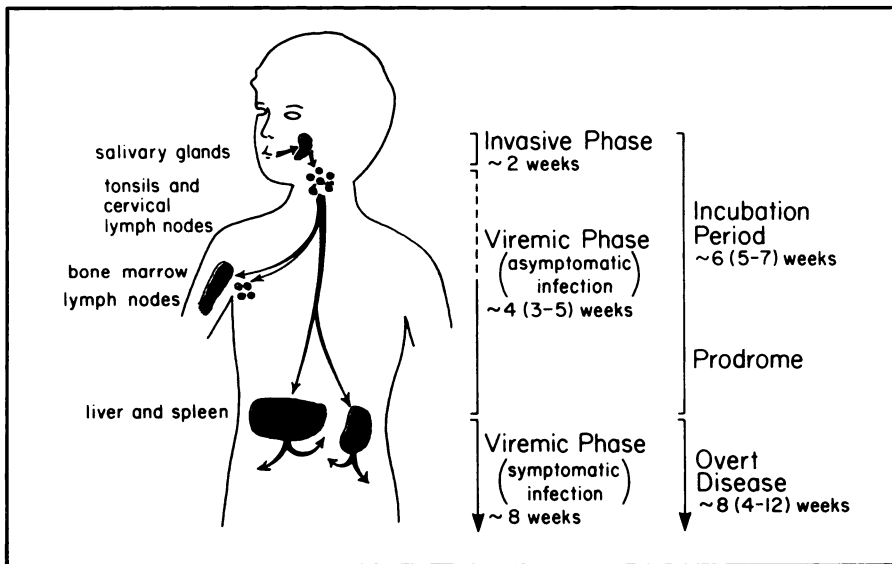


Fig 2. Pathogenesis of infectious mononucleosis. EB virus transmitted within saliva from infected individual to susceptible person. Incubation period includes initial period of about 2 weeks when virus replicates at local site in head and neck. Early invasive phase is followed by longer interval during which infectious virus is present in blood (viremic or vireocytemic phase). Unlike patients with most other viral infections, patient remains asymptomatic during first few weeks of viremic phase.

by others in large-scale seroepidemiologic studies. Finally, the riddle of infectious mononucleosis had been solved and an etiologic agent had been defined.

PATHOGENESIS

The exact pathogenesis of EB viral

infection remains to be defined. However, many clues have been obtained from seroepidemiologic investigations conducted over the last 30 years. Some of the most important observations were made by Hoagland, a physician at the US Military Academy at West Point, New York. He personally interviewed and ex-

amined all cadets who developed infectious mononucleosis. His most remarkable case involved a cadet who admitted to a brief liaison with a female student whom he met on a train on Dec 23, 1950. During their 12 hours together, they kissed frequently and also drank from the same bottles. The cadet became ill on Feb 8, 1951, while back at West Point. The female student, who had continued to correspond with the cadet, had become ill three days after their brief time together. Both cases were diagnosed as infectious mononucleosis. The incubation period between the index case (female student) and the secondary case (male cadet) was 47 days. Hoagland subsequently questioned 73 male cadets who developed infectious mononucleosis and discovered that 71 of 73 had a prior history of intimate oral contact 32 to 49 days before onset of symptoms. A naval physician also reported three sailors on board a ship who developed infectious mononucleosis 5 to 6 weeks after a brief shore leave. From the above studies, an incubation period of around 40 days seems to be about average when there is a history of intimate oral contact. When the disease is inadvertently transmitted by blood transfusion, the incubation period is about 2 weeks shorter.

From all of the above studies, a plausible schema for the pathogenesis of infectious mononucleosis has been drawn (Fig 2). The virus is presumably present in saliva, from which it enters the oral cavity and causes a localized infection. The site of this primary infection may be the salivary gland or possibly the adenotonsillar tissue. After about 2 weeks, the virus circulates in B lymphocytes throughout the body. During the initial 2 to 3 weeks of this viremia (or vireocytemia), the patient remains asymptomatic. Therefore, a prodrome is followed shortly by symptomatic disease. The viremic period probably includes multiple cycles of viral replication, which are finally terminated by the emergence of humoral and cell-mediated immune responses. A major portion of the symptomatology of infectious mononucleosis may be a manifestation of the immune response to the infection.

CLASSIC SYNDROME

A diagram of the classic infectious mononucleosis syndrome is presented in Fig 3. The onset is frequently heralded by the clinical symptoms described in the upper panel. Malaise and fatigue, together with sore throat, are present in virtually all patients in this group. The most common signs, as presented in the second panel from the top, are fever and adenopathy. Symmetrical, enlarged posterior cervical lymph nodes are most characteristic, although anterior cervical nodes may also be involved. In a few patients, the initial signs include a nonspecific exanthem. When these symptoms and signs are present in a teenaged patient, most pediatricians routinely order a hematologic profile and one of the heterophil agglutinin tests. In most instances, the differential white blood cell count will show a preponderance of lymphocytes, including large atypical lymphocytes or "Downey cells," (see Fig 4). The heterophil agglutination test or a test carried out using one of the new commercially available agglutination kits will usually produce positive findings when the disease is first clinically apparent, especially in children aged 4 years and older (Fig 1). As depicted in Fig 3, the titer of

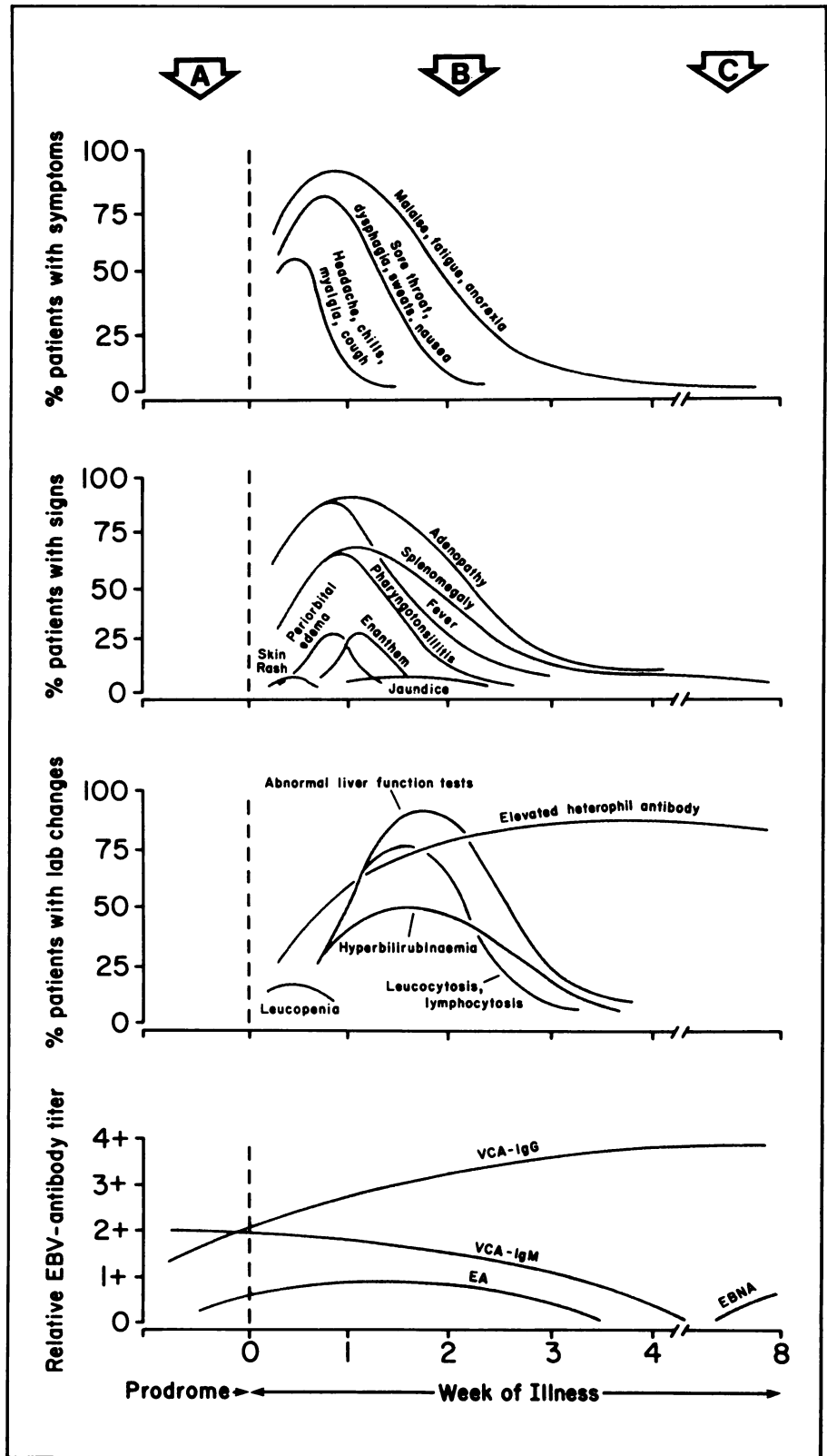


Fig 3. Clinical and laboratory manifestations of infectious mononucleosis. The predominant symptoms, signs, laboratory changes, and EB virus-specific serologic findings during classic infectious mononucleosis are depicted in four panels (from top to bottom, respectively). Arrow A indicates asymptomatic prodrome; arrow B, peak of clinical illness; and arrow C, early convalescence, during which the EB virus-associated neuropathies usually occur. (Some data derived from Carter RL, Penman HG(eds): *Infectious Mononucleosis*. Oxford, Blackwell Scientific Publishers, 1968, p 258.)

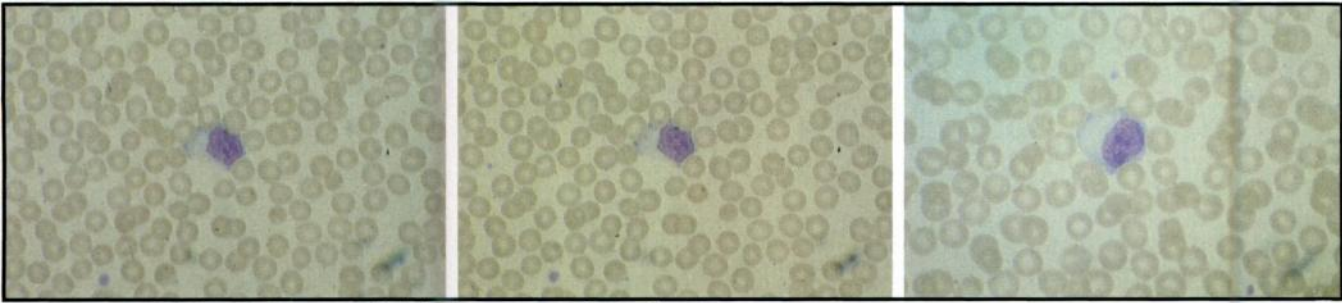


Fig 4. Downey cells from adolescent with infectious mononucleosis. Note large, eccentric nuclei with coarse chromatin and abundant basophilic cytoplasm which tends to flow around surrounding erythrocytes to give Downey cells an irregular shape. (Provided by Dr Barbara H. Tindle, Department of Pathology, University of Vermont College of Medicine, Burlington.)

heterophil antibody (whether measured by the traditional Paul-Bunnell test or rapid slide agglutination) remains high during the period of acute disease (Fig 3, arrow B), then it slowly falls to undetectable levels over the next 3 to 6 months. On occasion, heterophil antibody is still measurable as long as 1 year after onset of infectious mononucleosis.

Pharyngitis occurs in nearly all children with classic infectious mononucleosis. Because the clinical picture closely resembles bacterial disease, most of these children will have their throats cultured for the presence of group A β -hemolytic *Streptococcus*. The frequency of concomitant acute infectious mononucleosis and streptococcal throat infection has varied greatly from study to study, but the consensus appears to be that the concomitant bacterial disease is simply a reflection of its frequent occurrence in the general population. The streptococcal infection can be treated in the usual manner with oral penicillin or, as an alternative, erythromycin. Ampicillin should be avoided because of the strong association between the administration of ampicillin to a patient with infectious mononucleosis and the subsequent development within 1 week of a maculopapular rash. The rash is considered to be an immunologic phenomenon and abates when ampicillin is discontinued.

Hepatic involvement is also common during classic infectious mononucleosis. Although less than one quarter of the patients have hepatomegaly on physical examination, virtually all children with acute infectious mononucleosis have laboratory evidence of hepatic malfunction, with mild-to-moderate elevations in levels

of serum glutamic pyruvate transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT). These abnormalities in liver function, which are clinically apparent as jaundice in less than 10% of affected individuals, generally persist for 4 to 8 weeks before returning to pre-disease levels. This benign form of hepatitis does not evolve into chronic disease nor does it require any special treatment. More severe hepatic complications leading to hepatic failure are exceedingly rare and suggest a second diagnosis, such as a temporal association of infectious mononucleosis and Reye syndrome.

After recovery from infectious mononucleosis, there is usually lifelong immunity to clinical recurrence of disease. Presumably the maintenance of this immune state is dependent upon the permanent residence of latent EB virus within the lymphoreticular tissues. If the child subsequently develops a malignancy of any type and requires immunosuppressive therapy, the virus may reactivate and be excreted in the oropharynx. Recent clinical studies discussed below also suggest that a small portion of apparently healthy individuals who contract EB viral infection develop a chronic disease syndrome that persists for years.

DIFFERENTIAL DIAGNOSIS OF CLASSIC SYNDROME

Cytomegalovirus

As already mentioned, EB virus is one of five human herpesviruses. Infection with cytomegalovirus (CMV), one of the other agents in this group of viruses, can closely mimic the clinical manifestations of EB virus-associated infectious mononucleosis and

is the principal consideration in the differential diagnosis. The confusion between the two diseases is often compounded when both diseases are simply called "infectious mononucleosis" syndrome. It is the opinion of this author that the original appellation of infectious mononucleosis should be reserved for the heterophil-positive, EB virus-associated classic syndrome as described earlier in this text and also in Fig 3. In general, CMV infection is a milder febrile disease than EB virus-associated infectious mononucleosis. Cytomegaloviral disease may exhibit a similar hematologic profile, with large numbers of circulating atypical lymphocytes (hence, the name of CMV mononucleosis). Pharyngitis and cervical adenopathy are not always present and usually are milder than typically seen in EB virus-related illness. However, subclinical hepatitis is common in both CMV- and EB virus-associated diseases, as is splenomegaly. The main laboratory test for differentiation of the two diseases is the serum assay for heterophil agglutinins, because these antibodies are *not* produced by CMV infection. If the heterophil data are negative, further confirmatory tests for CMV include virus-specific serology and CMV isolation from saliva, urine, and buffy coat specimens.

Hepatitis Viruses

Other agents that may produce a hematologic mononucleosis syndrome include viral hepatitis and toxoplasmosis. Early viral hepatitis, including that due to hepatitis A virus and that due to hepatitis B virus, may closely resemble the prodrome of EB virus-related illness; however, neither

hepatitis virus causes the pharyngitis or adenopathy so commonly seen with EB viral infection, and the mononucleosis-like blood profile is short-lived. In addition, the degree of hepatic involvement with hepatitis A or B virus quickly becomes more extensive than commonly seen in EB viral disease; for example, levels of bilirubin rise above 10 mg/dL and transaminase values increase above 1,000 U/mL. Also, the heterophil test remains negative during hepatitis A or B infection. The definitive diagnosis of hepatitis A disease is made by detection of immunoglobulin M (IgM)-specific serum antibody; diagnosis of hepatitis B infection includes detection of hepatitis B surface antigen and antibody.

Toxoplasmosis

Another disease that occasionally causes a heterophil-negative mononucleosis-like blood picture is acute acquired toxoplasmosis. The patient is often febrile with prolonged malaise, sore throat, myalgia, and rash. Mild hepatomegaly and splenomegaly may also be present; severe jaundice is rare. The simplest method for diagnosis of acute toxoplasmosis is serologic, as the patients develop both IgM-specific and high-titer IgG-specific antibody responses which are easily measured.

In the above clinical situations, I have continued to emphasize the use of the heterophil test to discriminate EB virus-associated disease (heterophil-positive) from non-EB virus-related mononucleosis syndromes (heterophil-negative). This approach is useful for older children and teenagers who usually develop a heterophil antibody response during their acute EB virus infection. In children less than age 4 years, the classic syndrome is less frequently associated with acute EB viral infection. Therefore, EB virus-specific antibody titers must be obtained more frequently in order to make the correct diagnosis in the child with prolonged and unexplained fever. Whenever one of the neurologic, hematologic, or respiratory problems described in Table 1 is seen in a young, febrile child and other diagnoses are disproved, acute EB viral infection

should be considered. In addition to EB viral serologic studies, the virus can be cultured from throat secretions in virology laboratories with specialized facilities. Such studies usually require prior arrangements between the physician and the laboratory director.

SEROLOGIC DIAGNOSIS

Since the discovery that EB virus is the causative agent of infectious mononucleosis, several virus-specific diagnostic tests have been developed (Table 2). The most widely used is the immunofluorescence assay, which measures antibody to viral capsid antigen (VCA). Most patients with infectious mononucleosis already have detectable IgG antibodies against VCA prior to development of clinical symptoms. Many have IgM-specific anti-VCA antibody, in addition. The children also may exhibit antibody against EB virus-induced early antigen (usually the diffuse component). In contrast, anti-EBNA (Epstein-Barr nuclear antigen) antibody usually has not yet appeared when infectious mononucleosis is diagnosed. The diagnosis of acute infectious mononucleosis, therefore, can be made by the following criteria: IgM-specific anti-VCA (viral capsid antigen) antibody, antibody to early antigen (EA), and no antibody to Epstein-Barr nuclear antigen. In addition, most older children with acute infectious mononucleosis have positive findings on heterophil agglutination or rapid slide test (Fig 1). In convalescent sera, both the IgM anti-VCA response and the antibody to early antigen (EA) disappear, while antibody to nuclear antigen (EBNA) first appears during convalescence and then persists for life. It is the opinion of the author that virus-specific serology is not needed to confirm the diagnosis of infectious mononucleosis in a child with the classic syndrome, as illustrated in Fig 3, and a positive test for heterophil agglutinins.

CHRONIC INFECTIOUS MONONUCLEOSIS

Many pediatricians are aware that some of their patients with infectious mononucleosis complain of persist-

TABLE 1. Complications of Infectious Mononucleosis in 113 Children*

Clinical Problem	No.
Respiratory problems	
Pneumonia	6
Severe airway obstruction	4
Neurologic problems	
Seizures	4
Meningoencephalitis	2
Peripheral nerve palsy	1
Guillain-Barré syndrome	1
Hematologic problems	
Thrombocytopenia with hemorrhage	4
Hemolytic anemia	1
Jaundice	2
Glomerulonephritis	1
Orchitis	1
Other infections	
Bacteremia (group A streptococcal)	1
Recurrent tonsillopharyngitis	3

* Data from Sumaya and Ench.

TABLE 2. Major Viral Antigens to Which Antibody Responses Are Routinely Assayed

VCA	Viral capsid antigen
EA	Early antigen
EA-D	Early antigen-diffuse pattern
EA-R	Early antigen-restricted pattern
EBNA	Epstein-Barr (virus) nuclear antigen

ent symptoms for months and even years after the acute illness. Recently, Jones and colleagues examined a series of children and young adults with one or more of the following symptoms: fevers, pharyngitis, anterior cervical or generalized lymphadenopathy, arthralgia, myalgia, fatigue, depressive symptoms, dyslogia, headaches, and paresthesias (Table 3). The group included 18 children less than 15 years of age and 26 adults, among whom were 39 patients with EB viral antibody levels highly suggestive of active infection for at least 1 year. Most of the children had intermittent complaints, alternating with periods of feeling well. School performance of children in

TABLE 3. Clinical Findings and Reported Complaints Among 39 Patients with Suspected Chronic Infectious Mononucleosis*

Complaint	Patients	
	No.	(%)
Fatigue	29	(74)
Nervous system symptoms (headache/paresthesias)	28	(73)
Depression	27	(70)
Pharyngitis	25	(64)
Fever	24	(63)
Lymphadenopathy	23	(59)
Myalgia	21	(56)
Dyslogia	20	(53)
Arthritis/arthritis	19	(51)
Splenomegaly	9	(22)
Weight loss	9	(22)
Rash	5	(12)
Hepatomegaly	4	(10)

* Data from Jones et al.

either high school or college often dropped dramatically. One 16-year-old girl with mononucleosis developed a recurrent pattern of complaints which included malaise, fever, headaches, pharyngitis, abdominal pain, lethargy and depression. The disease pattern so disrupted her day-to-day functioning that she was unable to graduate from high school at the expected date. When she entered college, she also soon incurred difficulty performing to her usual standard. The case of a 6½-year-old boy was even more unusual. By his mother's records, he had had recurrent fevers up to 40°C (104°F) since the age of 3 months. These lasted 3 to 4 days at a time. A diagnostic evaluation at the age of 2 years was inconclusive. By 3 years of age, he had established a cyclical pattern of fever, pharyngitis, lymphadenopathy, palpebral edema, arthralgia, and malaise which persisted for the next 3 years.

When the sera from the above patients with an apparently chronic or recurrent course were analyzed for heterophil and EB virus-specific antibodies, the following results were obtained. None of the patients continued to have positive findings for heterophil agglutinins; however, 31 of 39 continued to have positive antibody titers against all three EB virus anti-

gens—VCA, EA, and EBNA. The other eight patients exhibited a more unusual antibody profile, with persistently elevated anti-EA antibody in the presence of very low or absent anti-EBNA. The latter pattern is unexpected in the otherwise normal individual with primary infectious mononucleosis and suggested some deficit in immunoregulation of the viral infection. A preliminary search for specific deficiencies in immune response was not productive. Although the above study does not yet conclusively demonstrate a chronic infectious mononucleosis syndrome, it does suggest that persistence of complaints following acute infectious mononucleosis ought to be carefully considered and recorded.

NEUROLOGIC MANIFESTATIONS

The neurologic sequelae of infectious mononucleosis have been estimated to occur in anywhere from 1% to 10% of all patients with primary illness. These neurologic sequelae fall into two patterns: the first are the CNS complications of the acute illness and the second are the neuropathies, which usually follow the acute illness by 2 to 3 months (Fig 3). The various manifestations of encephalitis related to infectious mononucleosis are listed in Table 4. The most dramatic CNS manifestation, especially in a teenaged individual, is acute psychosis. This syndrome was clearly described by Raymond and Williams in 1946. They reported the case of a college student who had been admitted to a psychiatric ward on December 11 because he had developed general malaise, fever, anorexia, fatigue, and headache. He had also noted swollen painful lymph nodes in his neck. Because of the above signs and symptoms, as well as mental confusion, he had been admitted to a local general hospital on December 1. During the succeeding ten days, he became progressively more irritable; his behavior was belligerent, impulsive, and unpredictable. For example, on one occasion he threw a glass of water in a nurse's face. Finally, he became delusional, with rambling speech that was frequently related to the patient's sexual exploits. Upon transfer to the psychiat-

ric hospital, he was again noted to be overactive and overtalkative, impulsive and unpredictable. His thought processes were rambling and irrelevant. Although he had no true hallucinations, his mood was extremely labile and his affect inappropriate. Among a battery of tests performed at the psychiatric hospital, it was discovered that his heterophil antibody test was strongly positive (1:1,792). Over the next weeks, his behavior alternated between intense excitement and overactivity to withdrawal from his environment. The behavior strongly resembled an acute schizophrenic episode. On December 19, there was an abrupt change in his symptomatology. He became alert and cooperative and the delusions disappeared. By December 23, he was sufficiently recovered to be discharged. Upon follow-up examination 3 months later, he was noted to be back to his normal social and scholastic life on the campus. This case report vividly illustrates the need to perform a heterophil antibody test on every teenager or young adult who develops an acute psychosis in the absence of a prior history of mental illness.

Copperman described another unusual psychiatric manifestation of infectious mononucleosis, the "Alice-in-Wonderland" syndrome (metamorphopsia). His three patients, two of whom were teenagers, had acute perceptual defects concerning the size, position, and distance of objects. The patients either felt that they were alternately shrinking and increasing in size, or else that objects or people in their environment were distorted in size and shape. All three patients had documented heterophil-positive infectious mononucleosis; in all three patients the syndromes resolved gradually as the acute disease abated.

The most common CNS sequela of infectious mononucleosis is meningoencephalitis. It is possible that the often subjective complaint of headache frequently noted with primary infection is, in fact, a manifestation of relatively minor CNS invasion by the virus. Encephalitis may occur in very young children, eg, both a 2-year-old and a 6-year-old child with EB virus-associated encephalitis were re-

ported by Grose and co-workers. The latter patient was initially seen with meningeal signs; upon examination of his CSF, 200 mononuclear cells per microliter were counted, of which 12% resembled large and atypical "Downey cells." Acute encephalitis associated with primary infectious mononucleosis may also present with temporal lobe signs, as indicated in Table 4. The neurologic disease cannot be differentiated from herpes simplex encephalitis on clinical grounds. Therefore, every child or young adult with symptoms suggestive of herpes simplex encephalitis should have at least a screening heterophil test prior to any invasive procedures or initiation of antiviral therapy. In one of the large vidarabine chemotherapy trials, 35 of 132 patients with encephalitis who had brain biopsies lacked evidence of herpes simplex infection. Of these 35, two patients were subsequently found to have EB virus infection.

Guillain-Barré syndrome is an ascending polyradiculoneuritis with the following clinical and laboratory findings: (1) dysesthesias of the feet or hands, or both, preceding the onset of paralysis; (2) rapid onset of symmetrical loss of muscle power in the upper or lower extremities, or both; (3) transient sensory losses; (4) frequent cranial nerve palsies, especially of the facial nerve; and (5) albuminocytologic dissociation in the CSF, ie, high protein content and low cell count. This syndrome, when it occurs in older children and teenagers, is strongly associated with a relatively recent EB viral infection. Unlike meningoencephalitis, which is virtually concomitant with the primary infection, Guillain-Barré syndrome usually follows the latter by 1 to 3 months. Occasionally, the non-CNS signs of infectious mononucleosis are not recognized at all until the onset of the polyneuropathy. The first case of Guillain-Barré syndrome and infectious mononucleosis was reported by Hiller and Fox in 1943. They described a 17-year-old female student with a 1-month history of malaise, abdominal pain, vomiting, enlarged cervical glands, and nuchal rigidity. Thereafter, she noted difficulty in swallowing and speaking, and a gradual, progressive inability to walk. Her

TABLE 4. Manifestations of Encephalitis Associated with Infectious Mononucleosis

Sign	Anatomic Localization
Hemiparesis/hemiplegia	Motor cortex, frontal lobe
Grasp reflex	Frontal lobe
Aphasia	Broca's area, frontal lobe
Psychosis/personality change	Temporal lobe
Hemianesthesia/ hemiparesthesia	Parietal lobe
Metamorphopsia (Alice-in-Wonderland syndrome)	Parietal lobe
Hemianopsia	Occipital lobe
Diplopia	Brainstem
Opisthotonus	Brainstem
Bilateral ptosis	Brainstem
Dysarthria	Brainstem
Syncope	Reticular activating system, brainstem
Chorea	Basal ganglia
Ataxia	Cerebellum
Nystagmus	Cerebellum
Dysmetria	Cerebellum
Explosive speech	Cerebellum

serum heterophil test was strongly positive. After a 4-week convalescence, she slowly regained her ability to eat, talk, and walk.

Thirty years later, Grose and Feorino expanded the association when they reported five patients (ages 1½, 4, 14, 16, and 27 years) with polyradiculoneuritis, all of whom had evidence of recent EB viral infection. Only two of the five had positive heterophil agglutinins in their serum at the time of neurologic disease. When Grose and Feorino studied a larger group of 24 children and young adults with Guillain-Barré syndrome, half had presumptive or definite serologic evidence of primary EB viral infection. Recent EB viral infection has also been associated with neuropathies of the peripheral and cranial nerves, including Bell's palsy. In most cases, the neurologic disease resolves with no permanent sequelae. However, permanent unilateral hearing loss was seen in one teenager with involvement of cranial nerve VIII during acute infectious mononucleosis.

INFECTIOUS MONONUCLEOSIS IN THE YOUNGER CHILD

Several groups in the United States, Israel, and Canada have attempted to define further the illness associated with infectious mononu-

cleosis in younger children. The symptoms and signs cited most often include fever and tonsillitis, lymphadenopathy, and hepatosplenomegaly. An occasional child has petechiae or ecchymoses, sometimes with thrombocytopenic purpura. Respiratory complaints are also frequently mentioned; however, it is not clear whether pneumonitis is caused by EB virus alone or by dual or sequential infection with EB virus and another respiratory pathogen. The incidence of the more severe complications found in a recent survey of 113 children 6 months to 16 years of age with documented infectious mononucleosis is presented in Table 1. Although not included in the table, two of the youngest patients (less than 1 year of age) in the series were considered to be in the "failure to thrive" category.

The younger the child at first acquisition of EB virus, the less likely is he or she to manifest clinical symptomatology. Children less than 2 years of age rarely have symptoms that are sufficiently definitive to lead to the appropriate viral diagnostic tests; the majority simply have fever as their main symptom. Peripheral blood smears, if taken, often show numbers of the atypical lymphocytes so characteristic of infectious mononucleosis in the older child. However,

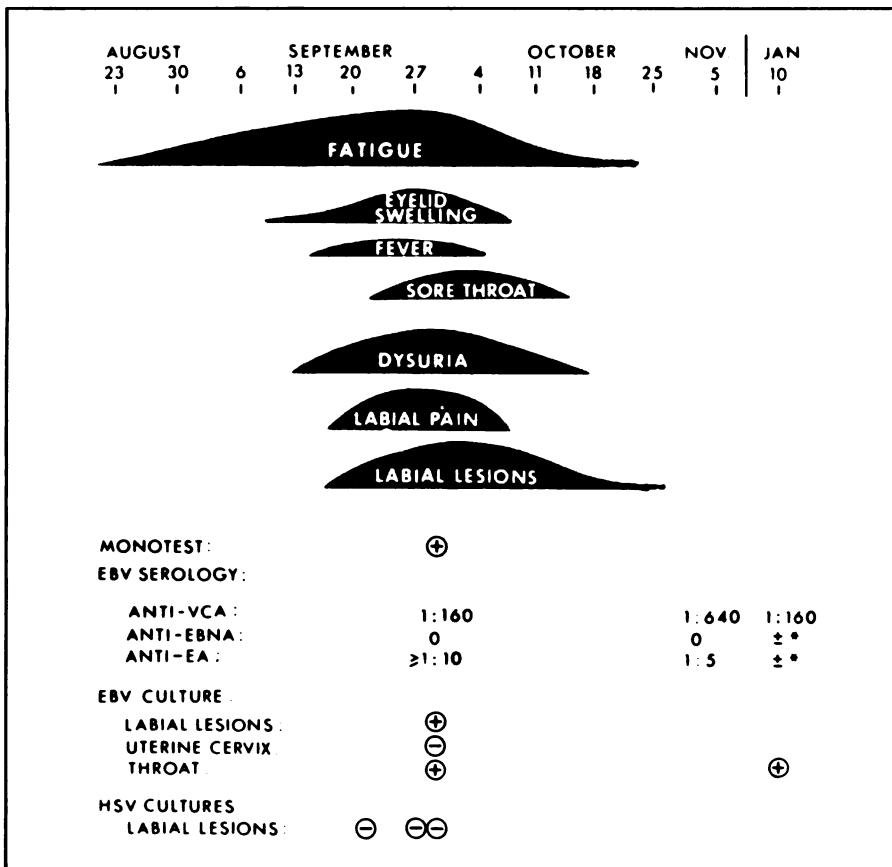


Fig 5. Diagrammatic representation of infectious mononucleosis in young woman with concomitant genital disease. Clinical symptoms and signs are depicted in top half of figure. Results of laboratory tests and viral cultures are indicated in bottom half of figure. (Reprinted with permission from Portnoy J, Ahronheim GA, Ghibu F, et al: Recovery of Epstein-Barr virus from genital ulcers. *N Engl J Med* 1984;311:967.)

heterophil agglutinins are detected in fewer than 30% of such children less than age 2 years, whereas about 75% who are between the ages 2 and 4 years develop such antibodies; more than 90% who are older do so.

GENITAL DISEASE

A most provocative case report has recently described an association between labial ulcerations and acute infectious mononucleosis. The patient was a 23-year-old woman who first became ill on August 23. The first symptom was fatigue. Vulvar pain and burning dysuria began on September 16. When the malaise, fatigue, and genital symptoms persisted, she was examined on September 21 and found to have three tender labial ulcerations. Cultures were negative for herpes simplex virus and *Chlamydia*. A WBC count of 11,100/ μ L was remarkable for a lym-

phocytosis: 28 neutrophils, 40 lymphocytes, 24 atypical lymphocytes, five monocytes, two eosinophils, and one basophil. A slide agglutination test was positive for infectious mononucleosis. Subsequent cultures from both the throat and the labial ulcerations were positive for EB virus as determined by transformation of cord blood leukocytes. The remainder of the clinical and laboratory findings are shown in Fig 5. The authors conclude that EB viral infection should now be included in the differential diagnosis of genital ulcerations.

This latest communication tends to corroborate an earlier similar report of a 14-year-old girl who developed an extensive vesiculoulcerative eruption on the labia after a 1-week history of low-grade fever, sore throat, and headache. A heterophil-test was positive at a dilution of 1:448. Multiple cultures of the lesions did not demonstrate herpes simplex virus even

through the lesions continued to be painful, with an associated discharge. The genital symptoms persisted for 2 weeks. Attempts were never made to culture EB virus from the genital ulcerations. This case, although less well documented, is strikingly similar to the one described above.

FATAL INFECTIOUS MONONUCLEOSIS

Fatal infectious mononucleosis rarely occurs in otherwise healthy children. Rare causes of mortality include neurologic complications, splenic rupture and hemorrhage, and bacterial or fungal sepsis. The neurologic manifestations of infectious mononucleosis have been discussed in an earlier section. Nearly all of the deaths in this group were due to respiratory failure associated with Guillain-Barré syndrome. With modern intensive care facilities, this cause of death can be avoided. The deaths due to bacterial or fungal sepsis occurred in patients with infectious mononucleosis who had secondary immunologic or hematologic deficits, eg, severe neutropenia or pancytopenia. These patients require appropriate antibacterial or antifungal therapy until the deficiency, usually transient, has resolved.

Splenic rupture usually occurs between the second and fourth weeks of illness. The rupture may first become manifest as acute hypotension; alternately, hemorrhage can occur over several days, often accompanied by abdominal pain. If the diagnosis is suspected, ultrasound examination and, if necessary, exploratory laparotomy should be considered immediately. Even though several cases of splenic rupture have been reported, there is no consensus about whether the ruptures usually occur spontaneously or as the result of traumatic episodes. There also is no consensus concerning the length of time children convalescing from infectious mononucleosis should avoid physical activities. A reasonable recommendation may be for affected individuals to defer any physical training for one month, to avoid vigorous athletic activities for 2 to 3 months, and to avoid strenuous contact sports for up to 6 months.

X-LINKED LYMPHOPROLIFERATIVE SYNDROME

The X-linked lymphoproliferative syndrome is also a cause of fatal infectious mononucleosis. In this syndrome, there is an unusual susceptibility to EB viral infection, inherited as an X-linked recessive phenomenon. This disease closely resembles several other X-linked immunodeficiency syndromes, eg, Wiskott-Aldrich syndrome, chronic granulomatous disease, and certain dysgammaglobulinemias. Young boys with X-linked lymphoproliferative syndrome develop a severe, often fatal, lymphoproliferative process after acute infectious mononucleosis. The usual cause of death is hepatic failure, complicated by bleeding and infection. At autopsy, prominent lymphocytic infiltrates are present in the liver, bone marrow, and other organs. When this diagnosis is being considered, the physician should question the parents about any other male children of theirs or relatives who may have died of "leukemia" or lymphoma. Generally, kindred studies of a documented case of EB virus-related X-linked lymphoproliferative syndrome will uncover other male children who suffered from other hematologic/immunologic dyscrasias, eg, hypogammaglobulinemia, agranulocytosis, and aplastic anemia. Because these affected children do not always produce antibodies to EB virus in high-titer, diagnosis may require identification of the virus in biopsy samples of tissue. At the present time, there is no specific treatment for this illness, although the antiviral agent acyclovir has been administered to several patients with mixed results.

AIRWAY OBSTRUCTION

The most common medical emergency resulting from infectious mononucleosis is acute upper airway obstruction. In a 10-year retrospective survey at Children's Hospital of Pittsburgh, 61 children were admitted because of the sequelae of infectious mononucleosis. The single most common condition was airway obstruction in 22 patients. Of these 22 children, 13 were less than 5 years

old and 9 were 6 years of age or older. An illustrative case was that of a 3-year-old girl with a four-day history of sore throat and progressive dysphagia. Her cervical lymph nodes were greatly enlarged and her spleen tip was palpable. A heterophil rapid slide test was positive. Otorhinolaryngologic examination revealed markedly hypertrophied and inflamed tonsils, with inspiratory stridor and obvious airway obstruction. The adenotonsillar hypertrophy and airway obstruction were confirmed by a lateral roentgenogram of the neck.

The following regimen has been used successfully by Snyderman at the Pittsburgh Children's Hospital Otolaryngology Service to treat airway obstruction secondary to infectious mononucleosis. Initially, the children are hydrated with intravenous fluids to replace prior and continuing losses. Decadron (dexamethasone sodium phosphate, 1 mg/kg) up to 10 mg is given as a loading dose by injection or intravenous infusion; thereafter, half of the loading dose of Decadron is parenterally administered every six hours for the next two to three days. The airway obstruction is handled by placement of a soft plastic airway through the nares into the trachea past the vocal cords. Placement of these tubes does not require anesthesia but does require the skills of an intensivist or otorhinolaryngologist. The same tube can remain in place for three days before removal or replacement. In most instances of acute airway obstruction secondary to infectious mononucleosis, the adenotonsillar hypertrophy should be sufficiently reduced after two to three days of corticosteroid therapy that tube replacement is unnecessary.

In a more emergent situation or in a setting in which the technical skill is not as available, the airway obstruction can be ameliorated by passage of an oropharyngeal tube. These tubes are somewhat more traumatic to the pharynx than a nasopharyngeal tube and are more easily dislodged. Of course, the child still requires treatment with systemic corticosteroids within an intensive care facility. Most intensivists avoid emergency tracheostomy because of the many attendant complications. Emer-

gency tonsillectomy is also discouraged because of frequent problems with bleeding postoperatively.

THERAPEUTIC MODALITIES

Corticosteroids

Other than for amelioration of acute airway obstruction, the debate over the use of steroids for treatment of acute infectious mononucleosis continues. Hoagland originally reported the routine administration of corticosteroids to West Point cadets with infectious mononucleosis who had unusually severe pharyngotonsillitis or who continued to have symptoms beyond the 14th day of illness. He did not report any adverse effects. Since that time, there have been several investigations into the effects of corticosteroids on the symptomatology of infectious mononucleosis. Although the quality of the controls for the different studies were variable, the studies generally demonstrate that the administration of corticosteroids to young adults (usually college-aged populations) almost always reduces the degree and the duration of major symptoms. One blinded trial by Bolden in England compared three regimens: (1) aspirin, (2) prednisone for six days and lactose for six days, and (3) prednisone for 12 days. These patients also were assessed for psychologic disturbance initially and were followed for 1 year. Bolden demonstrated that regimen 3 (prednisone, initially at 40 mg/d for 12 days) significantly decreased the duration of fever by four days, the number of days with an abnormal white cell count, and the persistence of the heterophil response, when compared with either of the first two regimens. Bolden did not find differences among the three groups in their psychologic profiles (ie, the prednisone groups did not "feel better"), nor did he observe a relationship between corticosteroid treatment and reduction in number of palpable lymph nodes or reduction of abnormally elevated liver enzymes.

Prout and Dalrymple performed a similar study in 82 American college students with infectious mononucleosis. They observed that treatment with corticosteroids decreased the

duration of fever and the length of confinement in the college infirmary. They could not define differences in resolution of lymphadenopathy or splenomegaly between treated and untreated groups. Although they did not observe any severe sequelae from the steroids, they did note that an occasional student became symptomatic again when steroids were stopped ("rebound" phenomenon). Another US study also found that college students with infectious mononucleosis who received treatment with corticosteroids showed more rapid resolution of their pharyngotonsillitis than did their untreated peers. The consensus of the above reports is that short-term treatment with oral corticosteroids, usually about 40 mg of prednisone initially with tapering over the course of 1 to 2 weeks, reduces the severity of the symptomatology associated with acute infectious mononucleosis in teenagers and young adults. No specific adverse side effects of therapy have been reported, although early corticosteroid treatment may retard the development of anti-EBNA antibodies. Therefore, as with many other medical questions, the physician must make a therapeutic decision on an individual basis for each patient with infectious mononucleosis.

Acyclovir

Acyclovir (Zovirax) is an antiviral agent manufactured by the Burroughs Wellcome Company. It is a

synthetic purine analog which exerts its effect by acting as a selective substrate for certain viral enzymes. Thereby, the drug inhibits the multiplication of herpes simplex virus types 1 and 2 and also is efficacious in the treatment of infections with varicella-zoster virus. Studies of EB virus in tissue culture have demonstrated inhibition of viral replication by acyclovir, although the mechanism of its action is not well understood. Nevertheless, preliminary clinical trials of acyclovir for treatment of severe EB viral infection have been initiated by the Burroughs Wellcome Company. At the time of preparation of this article, specific recommendations cannot yet be formulated, because too few patients have been studied.

Interferons

The therapeutic use of interferons for EB viral infections has not been well explored. There are three principal types of interferon; these include interferon- α (leukocyte interferon), interferon- β (fibroblast interferon), and interferon- γ (immune interferon). Prior to recombinant DNA technology, little interferon was available for clinical studies. Because the genes encoding the interferons have now been cloned into bacterial and yeast plasmids, large quantities of the interferons should shortly become available for experimental treatment of various infectious diseases, including those caused by EB virus. If a physician considers treatment with

either acyclovir or one of the interferons, an infectious disease specialist should be consulted for the most current recommendations about these investigational protocols.

ACKNOWLEDGMENTS

The author dedicates this review to Werner and Gertrude Henle, in whose laboratory he spent many happy and fruitful hours as a Fellow in virology.

The author also thanks James Jones and Ciro Sumaya for helpful discussions.

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Pediatr. Rev. 1985;7;35-44

DOI: 10.1542/pir.7-2-35

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