EPIDEMIOLOGY BULLETIN

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"Pseudo" Infectious Mononucleosis—Virginia

During the past year the Division of Epidemiology has investigated two outbreaks of suspected infectious mononucleosis. In both cases the diagnosis was not confirmed by further laboratory testing. The outbreak summaries below serve to illustrate some of the diagnostic pitfalls for this common disease.

Outbreak #1: Infectious mononucleosis (IM) was diagnosed over a period of five weeks in nine of 64 children attending a day-care center. All were reported to be *monospot* test positive. Eight of nine tests were performed by a single technician in a physician's office; the ninth was performed in another physician's office. Investigation of this cluster included retesting, within six weeks of illness onset, of these nine children. Only one child had an antibody titer of $\geq$ 1:320 to the viral capsid antigen of Epstein-Barr virus (EBV-VCA), and none had a detectable titer by the oxcell hemolysin test, the usual heterophile confirmatory test for mononucleosis. It was concluded that the monospot test results had been false-positive. Based upon the observation of several breaches in technique by the physician's technician during performance of the *monospot* test, it was suspected that laboratory technique

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Figure 1. Slide Appearance and Interpretation for the Monospot Test

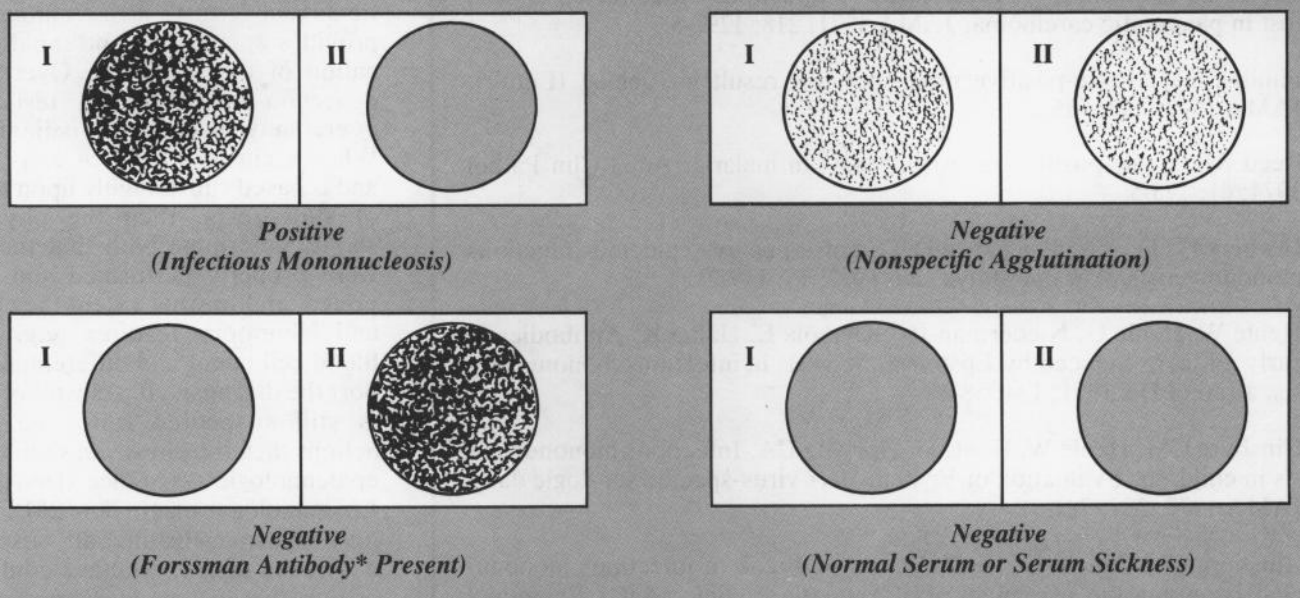

Figure 1. Interpretation of a rapid differential slide test for infectious mononucleosis, e.g. monospot. *Cell one, on the left, contains guinea pig antigen and cell two, on the right, contains beef erythrocyte stroma. Both cells contain the patient's serum and indicator cells (horse erythrocytes).*

**Present in ~ 10% of normal sera*

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contributed to these false-positive reactions.

Outbreak #2: A college physician diagnosed 285 cases of IM over a period of three months among a student body of approximately 4,000. *Monospot* tests, performed on only a few of the early cases, were all negative. Because the physician continued to suspect IM in these *monospot*-negative cases, he tested all 353 subsequent suspect cases for antibody to EBV-VCA and antibody to early antigen (EBV-EA), omitting the *monospot* tests. Testing cost for the commercial laboratory was in excess of $17,000. All but 68 of the 353 students had antibody to EBV-VCA and were thought to have IM. Fifty percent of students with antibody to EBV-VCA had titers ≥ 1:320 and 32% had antibody to EBV-EA.

Investigation of this outbreak included retesting of 94 students and testing of 75 students with mono-like illnesses not previously tested. Eighty-three percent of the 169 students for whom heterophile antibody was determined were tested within six weeks of illness onset. Only one student was found to have antibody by the ox-cell hemolysin (heterophile) test. It was concluded that the vast majority of antibody titers to EBV-VCA (including those ≥ 1:320) and EBV-EA were not indicative of recent EBV infection.

Editor's comment: The slide test for heterophile antibody (e.g. *Monospot* test) is relatively simple to perform and is now used by many physicians in their offices. It is both sensitive and specific for recent EBV infection. Properly performed, it has only rarely been reported to give false-positive results.[1-4] Misinterpretation or improper performance of the test can also yield false-positive results causing, in some cases, "pseudoepidemics".[5] Procedural errors which can yield false-positive results include mixing reagents in improper sequence, moving or rocking the slide during the reaction period, failure to use negative controls, and falsely interpreting equal agglutination in both squares of the slide as a positive reaction.

Given the sensitivity and specificity of a slide test such as *monospot,* it is usually unnecessary when diagnosing acute IM to test for antibody to the antigens of EBV. EBV titers are useful in determining prior exposure to EBV since one infection with EBV usually causes antibody to be present for life. Persistence of antibody, however, limits the usefullness of EBV titers for the diagnosis of acute IM. Even if paired sera are obtained, demonstration of a four-fold rise in titer is frequently impossible due to a relatively long interval between the onset of a patient's infection and presentation to his physician. Although earlier studies suggested that antibody to EBV-EA was indicative of recent infection,[6] recent experience indicates that this interpretation is no longer valid probably because newer laboratory techniques are more sensitive.

Testing for antibody to EBV-VCA was appropriately performed in the first outbreak reported above in order to exclude the possibility of heterophile antibody-negative EBV infection, which occurs more commonly in children.[7]

True outbreaks of IM are almost unheard of, probably because the virus is not very transmissable even though it may be excreted in saliva of infected persons for prolonged periods.[8] Rare outbreaks of IM may go unrecognized, the long incubation period (four to six weeks) making it relatively more difficult to link associated cases.

The diagnosis of IM is suspected whenever patients present with compatible clinical findings. For these patients a slide test, such as *monospot,* provides an accurate and rapid verification of the diagnosis. Overdependence on any laboratory test, however, may promote misdiagnosis. When a cluster of IM cases is noted and is based substantially upon results of slide tests, then the physician should determine both that the tests were properly performed and interpreted, and to what extent the clinical and laboratory features (e.g. white blood cell count and differential) support the diagnosis. If a cluster of cases is still suspected following these actions then the physician should seek epidemiologic assistance (Division of Epidemiology (804) 786-6261). It is only by investigating all suspected outbreaks of IM, whether confirmed or not, that we can learn more about the diagnosis and epidemiology of IM and mono-like illnesses.

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Update

Lyme Disease—United States

Lyme disease (LD) is a systemic, tick-borne illness that usually occurs during the summer. It was first recognized in 1975 in Connecticut (*1*). With the tick season approaching, public health officials and practitioners should be aware of recent advances in the microbiology, epidemiology, and treatment of this disease.

LD is characterized by a distinctive skin lesion, erythema chronicum migrans (ECM), often accompanied by nonspecific constitutional symptoms, such as fever, headache, myalgias, and arthralgias. ECM begins as a red macule or papule that expands to become an annular lesion, reaching up to 70 cm in diameter (*2*). Multiple skin lesions may occur. Some patients subsequently develop arthritic, neurologic, or cardiac complications weeks to months after the initial lesion. The arthritis is intermittent and usually involves large joints. Neurologic manifestations include Bell's palsy, meningoencephalitis, and peripheral neuritis; cardiac manifestations include myocarditis and atrioventricular conduction defects. Patients with the B-cell alloantigen, DR2, often have more severe and frequent late manifestations.

Early epidemiologic work suggested that LD's etiologic agent was transmitted by *Ixodes* ticks; subsequent studies confirmed that the distribution of known U.S. vectors—*I. dammini* ticks in the Northeast and Midwest and *I. pacificus* ticks in the West—parallels the distribution of U.S. cases. In 1982, a spirochete was isolated from an *I. dammini* tick (*3*). Subsequently, spirochetes were isolated from ECM skin lesions, blood, and spinal fluid of patients with LD (*4, 5*). The spirochete has recently been classified taxonomically as a *Borrelia* (*6, 7*).

LD diagnosis is primarily based on clinical criteria, and in endemic areas, the diagnosis can usually be made based on the characteristic ECM lesion and associated symptoms. However, atypical cases, cases presenting with only late manifestations, or cases occurring outside previously recognized endemic areas may be difficult to diagnose. Several laboratories have developed serologic tests for LD that can aid in the diagnosis. Laboratories at CDC and elsewhere currently use an indirect immunofluorescence assay (IFA) to measure antibodies against the spirochete. A titer of 256 or higher is considered positive, and the IFA appears to be highly specific, although patients with treponemal infections (syphilis, yaws, and pinta) may have false-positive titers. These latter patients have positive treponemal reagin tests, while patients with LD do not. The sensitivity of the LD test varies with the stage of the disease. When only ECM is present, as few as 50% of patients may have positive tests, while with complicated disease (when neurologic, arthritic, or cardiac symptoms are present), almost all patients will have positive tests (*8*).

Early treatment with tetracycline, penicillin, or erythromycin was previously shown to shorten the duration of ECM and to prevent or ameliorate late complicated disease. Recently, oral tetracycline 250 mg four times a day for 10 days has been suggested as the preferred therapy for patients with ECM (*9*). Longer or higher dose therapy or parenteral penicillin may be necessary for patients with more severe disease. The role of antibiotic therapy for the late arthritic phase of the disease is still being studied.

With the cooperation of state health departments, LD cases for 1980, 1982, and 1983 were reported to CDC. In 1980 and 1982, 226 and 487 cases, respectively, were reported (*10, 11*). A review of the still incomplete 1983 surveillance data indicates that over 500 cases occurred last year. Whether the increase in number of reported cases is due to increased recognition and interest in the disease or to a real increase in the incidence is unclear.

To better define the geographic distribution and the incidence of LD, state and territorial epidemiologists and CDC are collecting information on suspected cases of LD occurring in the United States each year. Healthcare providers are encouraged to report suspected cases to appropriate local and state health departments. Serologic testing of sera from suspected cases of LD is available at some state health departments or CDC. All sera should be submitted to the appropriate state health department with patients' clinical histories.

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Adapted from MMWR 1984;33:268-70.

Month: May, 1984

Disease	State				Mean 5 Year To Date	Regions				
	This Month	Last Month	Total to Date 1984	Total to Date 1983		This Month N.W.	N.	S.W.	C.	E.
Measles	0	0	2	21	93	0	0	0	0	0
Mumps	1	2	8	20	45	0	1	0	0	0
Pertussis	0	0	7	35	11	0	0	0	0	0
Rubella	0	0	0	1	34	0	0	0	0	0
Meningitis—Aseptic	6	7	46	54	38	1	1	1	1	2
Other Bacterial	18	18	119	123	96	2	3	7	3	3
Hepatitis A (Infectious)	9	13	46	53	94	1	2	5	1	0
B (Serum)	31	35	200	229	201	4	9	5	11	2
Non-A, Non-B	8	13	48	38	25	1	1	2	2	2
Salmonellosis	76	51	353	387	394	7	15	14	29	11
Shigellosis	6	15	108	57	212	0	3	1	0	2
Campylobacter Infections	46	38	178	159	71	13	10	3	11	9
Tuberculosis	27	30	160	171	0	0	0	0	0	0
Syphilis (Primary & Secondary)	37	25	180	246	251	2	7	5	15	8
Gonorrhea	1342	1354	7704	7709	8339	0	0	0	0	0
Rocky Mountain Spotted Fever	2	1	4	8	12	0	0	1	0	1
Rabies in Animals	18	21	117	341	112	10	8	0	0	0
Meningococcal Infections	3	11	34	42	41	0	1	0	0	2
Influenza	147	62	1088	848	1406	1	1	122	23	0
Toxic Shock Syndrome	1	3	5	4	3	1	0	0	0	0
Reyes Syndrome	0	3	4	5	10	0	0	0	0	0
Legionellosis	2	1	7	12	6	1	0	0	0	1
Kawasaki's Disease	3	0	6	25	12	1	1	0	1	0
Other:	—	—	—	—	—	—	—	—	—	—

Counties Reporting Animal Rabies: Alexandria 5 raccoons; Fairfax 2 raccoons; Fluvanna 1 raccoon; Loudoun 1 bat; Louisa 1 skunk, 1 fox, 1 bat, 3 raccoons; Madison 1 skunk; Rockingham 1 raccoon; Stafford 1 raccoon.

Occupational Illnesses: Occupational hearing loss 3; occupational pneumoconiosis 7; Asbestosis 3; Carpal tunnel syndrome 15; Metal fume fever 1.

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