

Prospective Study of the Natural History of Infectious Mononucleosis Caused by Epstein-Barr Virus

Thomas D. Rea, MD, MPH, Joan E. Russo, PhD, Wayne Katon, MD, Rhoda L. Ashley, PhD, and Dedra S. Buchwald, MD

Background: Knowledge regarding the clinical characteristics and natural history of acute infectious mononucleosis is based largely on older, often retrospective, studies without systematic follow-up. Differences in diagnosis, methodology, or treatment between historical and current practice might affect an understanding of this illness.

Methods: Using a prospective case series design, we enrolled 150 persons with an acute illness serologically confirmed as Epstein-Barr virus infection. The goal of the study was to assess symptoms, physical examination findings, laboratory tests, and functional status measures during the acute presentation and 1, 2, and 6 months later.

Results: Acutely, infectious mononucleosis was characterized by the symptoms of sore throat and fatigue and substantial functional impairment. Objective physical and laboratory examination findings included pharyngitis and cervical lymphadenopathy, a moderate absolute and atypical lymphocytosis, and mildly elevated transaminase levels. The traditional signs of fever and splenomegaly were relatively uncommon. By 1 month, most symptoms and signs and all laboratory tests had returned to normal. Fatigue, cervical lymphadenopathy, pharyngitis, and functional health status improved more slowly.

Conclusions: In contemporary practice most of the classical illness features of infectious mononucleosis are observed. Symptoms, signs, and poor functioning might be protracted in some patients. (J Am Board Fam Pract 2001;14:234–42.)

Infection with Epstein-Barr virus (EBV) has diverse clinical manifestations. In children, EBV infection is often asymptomatic, whereas in adolescents and young adults, it classically appears as infectious mononucleosis with fever, lymphadenopathy, and pharyngitis.^{1,2} Although infectious mononucleosis is typically self-limited and treated only with supportive care,¹ its duration and severity can vary considerably.^{2–14} Furthermore, most publications describing the natural history of infectious mononucleosis have been conducted in specialized populations; have incorporated nonstandard care; have evaluated only a limited number of biologic, psy-

chologic, and functional measures; or have failed to provide systematic follow-up.^{15–33} Finally, many studies were conducted before serologic tests for EBV were developed, bringing into question the actual composition of the study populations and the validity of subsequent findings.³⁴

To examine the natural history of infectious mononucleosis, we observed a population-based cohort enrolled in a large health maintenance organization for 6 months after the onset of serologically confirmed infection with EBV. During the initial illness and 1, 2, and 6 months later, we obtained subjective and objective measures of clinical and functional status. The goal of this study was to describe systematically and comprehensively the characteristics and course of infectious mononucleosis in the setting of current medical practice.

Methods

Study Setting

This study was conducted in a large health maintenance organization in the Puget Sound area that

Submitted, revised 31 January 2001.

From the Departments of Medicine (TDR, DSB), Psychiatry, Behavioral Sciences (JER, WK), and Laboratory Medicine (RLA), University of Washington, Seattle. Address reprint requests to Thomas D. Rea, MD, Pioneer Square Clinic, 206 3rd Ave South, Seattle, WA 98104.

This work was supported by grants RO1 AG08240 from the National Institutes of Mental Health and U19 AI38429 from the National Institute of Allergy and Infectious Diseases.

provides prepaid health care through facilities that include 2 hospitals, 23 outpatient medical clinics, 3 specialty centers, and a progressive care facility. The plan serves a heterogeneous socioeconomic population whose age and sex composition is similar to that of the western region of Washington State.

Participant Selection and Enrollment

Patients who met the following criteria were eligible for the study: (1) were 16 years of age or older; (2) had a positive heterophile antibody test; (3) reported the onset of symptoms within 14 days of having the heterophile test performed; (4) were not suffering from a chronic, disabling medical condition; (5) were not being treated with steroids; and (6) showed serologic evidence of acute EBV infection with a positive immunoglobulin M (IgM) titer to the viral capsid antigen. All laboratory records of the health maintenance organization were reviewed three times each week to search for patients who had a positive heterophile test. These potential participants were asked to join in a study of medical and psychologic factors involved in recovery from viral infections. Final determination of eligibility was based on information from the chart review, patient interview, and EBV serologic studies performed at the initial evaluation (see below). The recruitment and evaluation protocols were approved by the institutional review boards of the University of Washington and the health maintenance organization.

Participants were evaluated in person at the initial, 1-, 2-, and 6-month visits. Initial and follow-up visits included the administration of self-report measures, a physical examination, and laboratory tests. Participants received a psychiatric assessment at the initial evaluation.

Measures of Biological Disease Activity

A physical examination was performed at each visit. Participants were examined by a physician (DB) or a nurse trained in examination procedures and the detection of possible abnormalities for the presence of fever; rashes; pharyngitis; cervical, axillary, and inguinal adenopathy; hepatosplenomegaly; and jaundice. Lymph node size was noted in centimeters, and liver and spleen size was recorded qualitatively. For the purposes of analysis, fever was defined as a temperature of 37.5°C or higher, and lymphadenopathy was considered present when an-

terior cervical, axillary, or inguinal lymph nodes were 1 cm or larger and posterior cervical lymph nodes were 0.5 cm or larger. Pharyngitis was coded based on the presence or absence of pharyngeal or tonsillar erythema. Only patients with a palpable liver or spleen were deemed to have hepatomegaly or splenomegaly, respectively. A diagnosis of jaundice required the finding of scleral icterus.

A complete blood count, with a differential leukocyte count, serum transaminase levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), and bilirubin level were obtained using standard laboratory methods at each evaluation. A manual review of the differential leukocyte count was performed by the laboratory pathologist to ensure that atypical lymphocytes, if present, were detected and accurately quantified. Serologic testing for EBV that included IgG and IgM antibodies to the viral capsid antigen (VCA-IgG, VCA-IgM) was also performed at each study visit. Indirect immunofluorescence (with induced cells) using serial twofold dilutions was used to determine antibodies to VCA-IgG (1:10–1:1280) and VCA-IgM (1:10–1:40).³⁵ Titers for VCA-IgG and VCA-IgM were expressed as the reciprocal of the highest dilution to register a positive reaction and were considered positive if greater than 10.

Measures of Symptoms and Functional Status

Measures obtained at each visit were from the Symptom Checklist-90 (SCL-90) and the Medical Outcomes Study Short-Form General Health Survey (SF-36). The SCL-90, typically used to assess the presence and severity of somatic and psychologic complaints,³⁶ was modified to include those symptoms associated with infectious mononucleosis that were most frequently mentioned in previous publications and standard textbooks: fatigue, sore throat, painful lymph nodes, fever, sleeping too much, headache, sore muscles, nausea, sore joints, cough, and rash. Symptom severity on the SCL-90 was graded as 1 = not at all, 2 = a little bit, 3 = moderately, 4 = quite a bit, or 5 = extremely. Only responses of 3 or higher were used in calculating the frequency of symptoms.

To assess health-related functional status, we used the SF-36.³⁷ This instrument has the following eight subscales: general health, mental health, vitality, pain, physical and social functioning, and role limitations related to physical and emotional functioning. Each subscale is scored from 0 to 100

with higher scores indicating better function or less pain. Finally, the National Institute of Mental Health Diagnostic Interview Schedule (DIS)³⁸ was administered at enrollment to characterize current and lifetime psychiatric disorders. The DIS is a reliable and valid structured psychiatric interview yielding *Diagnostic & Statistical Manual of Mental Disorders: DSM-III-R* diagnoses.³⁹ The modules on major depression, panic, and generalized anxiety disorders were administered to all participants at the initial evaluation by research assistants trained in its use.

Results

Eligible persons who declined participation ($n = 111$) or could not be contacted despite multiple attempts ($n = 72$) were similar in age (22 ± 7 years) and sex (48% female) composition to the study participants. Of the 150 participants who were initially enrolled, 140 successfully completed all three follow-up evaluations. The average age of the participants was 21.3 years (range 16–46 years) and 53% were women. Most were single (93%), white (90%), and students (64%). Participants had a mean of 12.6 (SD ± 2.6) years of education. No participant required hospitalization for infectious mononucleosis during the course of the study. Using the DIS at baseline, the current and lifetime prevalence of depression (5% and 11%, respectively) and anxiety-panic disorder (2% and 3%, respectively) were generally low and comparable to an age-matched population.^{40–42}

The mean number of symptoms at each visit was 4.4 initially, 1.3 at 1 month, 1.0 at 2 months, and 0.9 at 6 months. Individual symptom frequencies at each visit are shown in Table 1. At the first visit, sore throat and fatigue were the most common symptoms and were experienced by about three quarters of the participants. At the 1-month follow-up visit, there was substantial diminution in the frequency of all symptoms, although 28% still experienced fatigue. Only a relatively small improvement in symptom frequency was observed at the 2-month visit. Fatigue remained the most prominent residual complaint. Although the frequencies of fatigue and sleeping too much declined modestly between the 2- and 6-month visits, the frequencies of other symptoms were relatively unchanged during this interval. By 6 months, most symptoms associated with infectious mononucleosis were reported by less than 10% of participants.

Table 1. Frequency of Symptoms of Infectious Mononucleosis at Four Time Points for 140 Patients Who Completed All Four Visits

Symptom	Initial No. (%)	1 Month No. (%)	2 Months No. (%)	6 Months No. (%)
Sore throat	104 (74)	22 (16)	16 (11)	16 (11)
Fatigue	108 (77)	39 (28)	29 (21)	18 (13)
Fever	63 (45)	3 (2)	3 (2)	2 (1)
Sleeping too much	64 (45)	26 (18)	20 (14)	12 (9)
Painful nodes	80 (57)	15 (11)	8 (6)	5 (4)
Headache	71 (50)	21 (15)	21 (15)	23 (16)
Rash	21 (15)	5 (4)	4 (3)	5 (4)
Cough	31 (22)	15 (11)	14 (10)	11 (8)
Sore muscles	39 (28)	19 (14)	16 (11)	15 (11)
Sore joints	33 (23)	21 (15)	9 (6)	13 (9)
Nausea	38 (27)	11 (8)	11 (8)	8 (6)

As shown in Table 2, at study entry, most participants had anterior cervical lymphadenopathy, posterior cervical lymphadenopathy, and pharyngeal inflammation, whereas 28% of participants were febrile. Less than 10% had hepatomegaly, splenomegaly, or extracervical (inguinal or axillary) lymphadenopathy. No participant was jaundiced. The cervical lymphadenopathy and pharyngitis resolved gradually during the course of the study but were still evident in approximately one quarter of participants at the 6-month follow-up visit.

Table 2 also displays the laboratory and serology results. An absolute, relative, and atypical lymphocytosis was found initially but had subsided by the 1-month visit. Platelet counts were typically normal during both the acute infection and the convalescent evaluations. As exhibited by elevated transaminase levels, more than one half of the participants had laboratory evidence of hepatitis when initially evaluated, which resolved in nearly all cases in the ensuing month. Elevations in bilirubin either initially or during follow-up period were rare (only 1 person had a value ≥ 2.5 mg/dL). All participants were positive for VCA-IgM (as required for study eligibility) and VCA-IgG during the acute infection. The IgG titer remained positive in all cases and had only a twofold median decrease during the 6 months of follow-up. Participants, however, steadily lost IgM reactivity, with only 13% being IgM positive by 6 months.

Finally, as shown in Table 3, scores on the social functioning, pain, vitality, and physical role limitations subscales of the SF-36 at the initial visit were

Table 2. Frequency of Physical Examination and Laboratory Findings in Infectious Mononucleosis at Four Time Points for 140 Participants Who Completed All Four Visits.

Finding	Initial	1 Month	2 Month	6 Month
Physical examination abnormalities, No. (%)				
Any cervical adenopathy	109 (77)	77 (55)	55 (39)	41 (29)
Anterior cervical adenopathy	87 (62)	56 (40)	33 (24)	28 (20)
Pharyngitis	103 (73)	66 (47)	29 (21)	35 (25)
Posterior cervical adenopathy	83 (59)	49 (35)	38 (27)	20 (14)
Temperature $\geq 37.5^{\circ}\text{C}$	39 (28)	23 (16)	16 (11)	14 (10)
Splenomegaly	11 (8)	4 (3)	0 (0)	0 (0)
Hepatomegaly	10 (7)	3 (2)	1 (1)	2 (1)
Axillary or inguinal adenopathy	7 (5)	2 (1)	2 (1)	1 (1)
Routine laboratory tests and serologic measures				
Lymphocytes/mm ³ , mean (median)	3,248 (3,060)	2,010 (1,984)	2,006 (1,961)	1,961 (1,925)
Lymphocyte %, mean (median)*	49 (49)	35 (36)	34 (34)	33 (32)
Atypical lymphocytes %, mean (median)*†	9 (8)	4 (3)	3 (2)	3 (2)
Platelets/mm ³ , mean (median)‡	279 (270)	239 (228)	241 (234)	238 (232)
SGOT >48 U/L, No. (%)	44 (31)	1 (1)	2 (1)	3 (2)
SGPT >42 U/L, No. (%)	86 (61)	7 (5)	4 (3)	4 (3)
Bilirubin >1.2 mg/dL, No. (%)	8 (6)	6 (4)	5 (4)	6 (4)
VCA-IgG titer, median	160	80	80	80
VCA-IgM titer, median	40	20	0	0

*Percent of total leukocyte count.

†A subset of 120 of the 140 participants had atypical lymphocytes manually quantified.

‡ $\times 1000$.^{||}Expressed as the reciprocal value.

indicative of moderate disability and distress. Functional status steadily improved across all domains and throughout the entire follow-up period.

Discussion

We prospectively and systematically evaluated the clinical aspects of acute EBV infection in a popu-

lation-based cohort of persons aged 16 years old or older who were cared for as outpatients with supportive, nonspecific measures.¹ The initial diagnosis of infectious mononucleosis was dependent on the finding of both a positive heterophile antibody and VCA-IgM titers in the setting of acute symptoms. During the acute phase, infectious mononu-

Table 3. Functional Status in Infectious Mononucleosis at Four Time Points for 140 Participants Who Completed All Four Visits.

SF-36 Subscale	Mean Score (\pm SD)*			
	Initial	1 Month	2 Months	6 Months
General health	69 (± 18)	71 (± 19)	72 (± 19)	73 (± 19)
Physical functioning	70 (± 21)	84 (± 16)	90 (± 12)	93 (± 10)
Social functioning	48 (± 25)	72 (± 26)	82 (± 21)	87 (± 20)
Emotional well-being	66 (± 18)	71 (± 17)	72 (± 17)	76 (± 17)
Pain	51 (± 25)	79 (± 21)	85 (± 17)	89 (± 15)
Vitality	33 (± 19)	50 (± 21)	60 (± 20)	66 (± 20)
Physical role limitation	21 (± 29)	55 (± 43)	77 (± 34)	88 (± 28)
Emotional role limitation	62 (± 41)	70 (± 40)	78 (± 36)	85 (± 30)

*Range from 0 = poorest function to 100 = best function.

SF-30—Medical Outcomes Study Short-Form General Health Survey.

cleosis was characterized by the symptoms of sore throat, fatigue, and substantial functional impairment; objective physical and laboratory examination findings of pharyngitis; cervical lymphadenopathy; a moderate absolute and atypical lymphocytosis; and mildly elevated transaminase levels. The traditional signs of fever and splenomegaly were relatively uncommon. By 1 month most symptoms and signs and all laboratory tests had returned to normal. Fatigue, cervical lymphadenopathy, pharyngitis, and functional health status improved more slowly than other parameters.

Our methods stand in contrast to those of previous studies that have had one or more methodologic limitations. First, previous publications often focused on unique samples (eg, military recruits) or hospitalized patients who received multiple evaluations during the acute phase, but few or none during convalescence.^{15–33} Second, older research was frequently retrospective or had methods that were not clearly stated.^{15,20–24,28–31} Third, surrogate hematologic or serologic markers were often relied on to diagnose infectious mononucleosis. Finally, some investigations that described infectious mononucleosis illness features used treatment with antiviral, antibiotic, or steroid medications.^{17–19,32} Such differences in definition, study design, or care could have a major impact on the reported characteristics and clinical course of infectious mononucleosis.

Demographics

As in other studies,^{2,15,17,28} we found that infectious mononucleosis predominantly affected unmarried, young, white adults with men and women in comparable proportions. Moreover, students comprised nearly two thirds of our participants. Although a student predominance among persons with infectious mononucleosis is typically assumed, this observation, with few exceptions,^{28,43,44} has been a product of selection factors imposed by previous study designs.

Acute Illness

In his classic work on infectious mononucleosis among military personnel, Hoagland² concluded that the “subjective manifestations of IM are characteristic, but far from specific.” He and others noted that the hallmark symptom of infectious mononucleosis was sore throat, occurring in approximately 80% of persons.^{2,15,19,29} Several stud-

ies reported that about 50% of patients also had malaise, painful lymph nodes, headache, and subjective fever.^{2,28,29} Cough, rash, arthralgias, myalgias, nausea, and somnolence were unusual symptoms (ie, < 10%).^{2,15,28,29,33} We found that sore throat and fatigue were reported by approximately 75% of patients when initially examined, whereas subjective fever, headache, and lymphadenopathy were noted by about 50%. Surprisingly, so-called uncommon symptoms, such as cough, sore joints, and nausea, were reported by a quarter of participants, suggesting that these symptoms might not possess the negative predictive value for infectious mononucleosis previously ascribed to them.²

Our physical examination results were generally consistent with published reports of acute infectious mononucleosis in which cervical lymphadenopathy, pharyngitis, and fever were observed in most of the patients (75%–100%);^{2,20,22,27,29,44,45} splenomegaly was variably detected (25%–75%), and rash, hepatomegaly, and jaundice were infrequently reported (<10%). Among our study participants, however, fever and splenomegaly were relatively uncommon (28% and 10%, respectively) perhaps because, in contrast to most other investigations, our study participants were not repeatedly assessed during the acute phase. Previous studies that have conducted only a few initial assessments have revealed a similarly small proportion of febrile patients.^{18,27,46} Alternatively, because fever in infectious mononucleosis peaks for 5 to 7 days then gradually returns to normal,¹ the interval between diagnosis and the study evaluation (typically < 1 week) might account in part for the relatively low rate of fever we observed. Thus, the absence of fever or splenomegaly on a single occasion should not deter clinicians from pursuing a diagnosis of infectious mononucleosis. Finally, this study confirms the common occurrence of posterior cervical lymphadenopathy (59%), a finding that has been debated as being characteristic of acute infectious mononucleosis.^{2,46}

The differential leukocyte count plays an important, although unsettled, role in the diagnosis of infectious mononucleosis. One early criterion for diagnosis required an absolute lymphocytosis of more than 4,500/mL, a differential leukocyte count with more than 50% lymphocytes, and the presence of a great many atypical lymphocytes.² Another considered the diagnosis only when atypical lymphocytes comprised more than 20% of the total

leukocyte count.⁴⁷ During the initial examination, we observed a mean absolute lymphocytosis of 3,248/mL and lymphocyte fraction of 49%, with atypical lymphocytes constituting, on average, 9% of total leukocytes. Explanations for the consistently lower frequency of such abnormal values in our study are the single measurement at each time point and the aforementioned use of strict hematologic selection or entry criteria in some previous investigations.^{2,15,22,47} Similar to other studies of infectious mononucleosis, most of our sample had mildly abnormal serum transaminase levels in the absence of overt clinical hepatitis.^{21,22,28,45} Finally, none of the participants in this study experienced complications of infectious mononucleosis, such as splenic rupture, encephalitis, Guillain-Barré syndrome, agranulocytosis, or severe thrombocytopenia.^{2,3,6,8,9,48,49}

Convalescence

Descriptive, longitudinal studies on illness resolution after acute infectious mononucleosis using standardized assessments are lacking. Although symptoms associated with the acute illness typically resolve in the first month,^{15,17,18,22,24,29,31} a prolonged recovery period associated with clinical and laboratory sequelae has been reported in the medical literature.^{26,29,31} An early description of “chronic mononucleosis syndrome” cited “weakness, aching legs, low-grade fever, and depression” as typical symptoms.¹² More recently, a prospective study of EBV-induced glandular fever showed that 9% of patients developed a syndrome of chronic fatigue up to 6 months after illness onset.⁵⁰ Still others have reported unusual hematologic or immunologic responses among patients with persistent symptoms after infectious mononucleosis.^{51–53}

We found that symptoms had generally resolved by the 1-month visit; after 2 months there was little further improvement. Fatigue and sleeping too much abated more slowly than other symptoms, however, and continued to improve between the 2- and 6-month assessment. It is unknown whether the 10% prevalence of most symptoms at 6 months reflects the underlying frequency of these symptoms in the general population⁵⁴ or, alternatively, a small and enduring excess of postinfectious mononucleosis symptoms.

In terms of objective findings, we found that pharyngitis and cervical lymphadenopathy were evident in a substantially larger fraction of partici-

pants than the corresponding symptoms of sore throat and painful lymph nodes at each point during follow-up. Although more prolonged laboratory abnormalities after infectious mononucleosis have been noted,²⁸ our results concur with investigations that have reported such findings typically resolve in 2 to 4 weeks.^{2,17,19,29} For example, transaminase levels and the differential leukocyte counts had largely returned to normal by the 1-month evaluation and subsequently remained stable. During the acute period, all participants were positive for VCA-IgG, and congruent with other studies,^{19,32,34} all remained VCA-IgG positive with only a modest decrease in titer during the subsequent 6 months. VCA-IgM titers declined more rapidly in a pattern consistent with other investigations,^{19,32,34} although 34% and 13% were still positive at 2 and 6 months, respectively.

Systematic measurement of functional status has not been previously obtained among patients with infectious mononucleosis. In this study, the SF-36 scores obtained during acute infection were indicative of a moderate but widespread impact on social, physical, and emotional aspects of functioning. Although a relatively greater proportion of recovery came in the first month, functional health status consistently improved in all domains throughout the follow-up period. The limitations reflected by SF-36 scores better characterize the incapacity noted among persons diagnosed with glandular fever caused by EBV infection⁵⁵ and anecdotal reports of withdrawal from school or prolonged work absence as consequences of delayed recovery from infectious mononucleosis.^{21,26}

This study has several limitations. First, the selection of participants relied on a positive heterophile antibody test that was ordered based on clinical discretion. Thus, factors such as providers' understanding of infectious mononucleosis and time constraints could affect their use of this test, most likely excluding those with unusual or less severe symptoms and signs of infection.⁷ Second, the heterophile antibody test can infrequently be either falsely positive or negative. A few patients with a non-EBV mononucleosis-like illness might test positive for heterophile antibody; most, if not all, of these false-positive tests would be appropriately excluded by a negative VCA-IgM.³⁴ In addition, false-negative responses occur in up to 10% of nonpediatric cases of EBV infectious mononucleosis. Because a positive heterophile antibody test was

required to be eligible for this study, our findings might not reflect the illness characteristics seen in the few persons with heterophile-negative, acute EBV infection. Third, the interval between the time of diagnosis and the initial study evaluation could have affected measures taken during the acute illness.

Ideally, participants would be enrolled before the onset of infectious mononucleosis and observed longitudinally, but the costs and logistics of such an endeavor are prohibitive. Of importance, however, all our participants had been ill for 14 days or less and were still acutely symptomatic at their initial study visit. Finally, because our study design excluded a few patients with certain characteristics (chronic disabling medical illness, initial steroid treatment) and precluded enrolling persons with infectious mononucleosis who did not seek medical care, our results might not be generalizable to all persons with infectious mononucleosis.

In summary, in our population-based study, infectious mononucleosis usually affected young, single, white, students without a sex predilection. When the patients were first encountered, infectious mononucleosis was characterized by symptoms of sore throat and fatigue, cervical lymphadenopathy and pharyngitis on examination, and substantial social, emotional, and physical functional disability. Typical laboratory findings consisted of a moderate absolute and atypical lymphocytosis, normal platelet count, and mildly elevated transaminase levels. Notably, the traditionally uncommon symptoms of cough, sore joints, nausea, and sore muscles were present in a substantial minority, whereas the classical signs of fever and splenomegaly were relatively infrequent manifestations. During convalescence, most symptoms and all laboratory test results had returned to normal by 1 month. Fatigue, cervical lymphadenopathy, pharyngitis, and functional health status, however, improved more slowly. Further studies are needed to understand the process of recovery in infectious mononucleosis. For now, the results of the current study can be used to educate and reassure patients that the persistence of some symptoms and signs many months after acute infection should not be unexpected.

The authors wish to thank Dr. Anthony Komaroff for his advice and review of the manuscript.

References

1. Schooley RT, Dolin R. Epstein-Barr virus (infectious mononucleosis). In: Mandell GL, Douglas RG Jr, Bennett JE, editors. Principles and practice of infectious diseases. New York: Churchill Livingstone, 1990:1172-85.
2. Hoagland RJ. Infectious mononucleosis. New York: Grune & Stratton, 1967.
3. Clarke BF, Davies SH. Severe thrombocytopenia in infectious mononucleosis. *Am J Med Sci* 1964;248:703-8.
4. Radel EG, Schorr JB. Thrombocytopenic purpura with infectious mononucleosis. Report of 2 cases and a review of the literature. *J Pediatr* 1963;63:46-60.
5. Grossman LA, Wolff SM. Acute thrombocytopenic purpura in infectious mononucleosis. *JAMA* 1959;171:2208-10.
6. Grose C, Henle W, Henle G, Feorino PM. Primary Epstein-Barr virus infections in acute neurologic diseases. *N Engl J Med* 1975;292:392-5.
7. Auwaerter PG. Infectious mononucleosis in middle age. *JAMA* 1999;281:454-9.
8. Bernstein TC, Wolff HG. Involvement of the nervous system in infectious mononucleosis. *Ann Intern Med* 1950;33:1120-38.
9. Neel EU. Infectious mononucleosis. Death due to agranulocytosis and pneumonia. *JAMA* 1976;236:1493-4.
10. Dagan R, Powell KR. Postanginal sepsis following infectious mononucleosis. *Arch Intern Med* 1987;147:1581-3.
11. Finkel M, Parker GW, Fanslau HA. The hepatitis of infectious mononucleosis: Experience with 235 cases. *Mil Med* 1964;129:533-8.
12. Isaacs R. Chronic infectious mononucleosis. *Blood* 1948;3:858-61.
13. White PD, Thomas JM, Amess J, Grover SA, Kangro HO, Clare AW. The existence of a fatigue syndrome after glandular fever. *Psychol Med* 1995;25:907-16.
14. Smith JN. Complications of infectious mononucleosis. *Ann Intern Med* 1956;44:861-73.
15. Evans AS. Infectious mononucleosis in University of Wisconsin students. Report of a five-year investigation. *Am J Hyg* 1960;71:342-62.
16. Niederman JC, McCollum RW, Henle G, Henle W. Infectious mononucleosis. Clinical manifestations in relation to EB virus antibodies. *JAMA* 1968;203:205-9.
17. Tynell E, Aurelius E, Brandell A, et al. Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study. *J Infect Dis* 1996;174:324-31.
18. van der Horst C, Joncas J, Ahronheim G, et al. Lack of effect of peroral acyclovir for the treatment of acute infectious mononucleosis. *J Infect Dis* 1991;164:788-92.

19. Andersson J, Britton S, Ernberg I, et al. Effect of acyclovir on infectious mononucleosis: a double-blind, placebo-controlled study. *J Infect Dis* 1986; 153:283–90.
20. Joncas J, Chiasson JP, Turcotte J, Quennec P. Studies on infectious mononucleosis: clinical data, serologic and epidemiologic findings. *Can Med Assoc J* 1968;98:848–54.
21. Dunnet WN. Infectious mononucleosis. *Br Med J* 1963;1:1187–91.
22. Mason WR Jr, Adams EK. Infectious mononucleosis: an analysis of 100 cases with particular attention to diagnosis, liver function tests and treatment of selected cases with prednisone. *Am J Med Sci* 1958; 236:447–59.
23. Hoagland RJ. Infectious mononucleosis. *Am J Med* 1952;13:158–71.
24. Hoagland RJ. The clinical manifestations of infectious mononucleosis: a report of two hundred cases. *Am J Med Sci* 1960;240:55–63.
25. Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children. I. Clinical and general laboratory findings. *Pediatrics* 1985;75:1003–10.
26. Thompson DS, Godleski J, Herman S. Prognosis post infectious mononucleosis. *J Am Coll Health Assoc* 1969;17:453–7.
27. Dalrymple W. Infectious mononucleosis. 2. Relation of bed rest and activity to prognosis. *Postgrad Med* 1964;35:345–9.
28. Stevens JE, Bayrd ED, Heck FJ. Infectious mononucleosis: a study of 210 sporadic cases. *Am J Med* 1951;11:202–8.
29. Contratto AW. Infectious mononucleosis: a study of one hundred and ninety-six cases. *Arch Intern Med* 1945;73:449–59.
30. Hobson FG, Lawson B, Wigfield M. Glandular fever: a field study. *Br Med J* 1958;12:845–52.
31. Milne J. Infectious mononucleosis. *N Engl J Med* 1945;233:727–31.
32. Andersson J, Skoldenberg B, Henle W, et al. Acyclovir treatment in infectious mononucleosis: a clinical and virological study. *Infection* 1987;S1:S14–20.
33. Read JT, Helwig FC. Infectious mononucleosis. *Arch Intern Med* 1945;75:376–80.
34. Evans AS, Niederman JC, Cenabre LC, West B, Richards VA. A prospective evaluation of heterophile and Epstein-Barr virus-specific IgM antibody tests in clinical and subclinical infectious mononucleosis. Specificity and sensitivity of the tests and persistence of antibody. *J Infect Dis* 1975;132:546–54.
35. Andiman WA. EBV. In: Schmidt NJ, Emmons RW, editors. *Diagnostic procedures for viral, rickettsial, and chlamydial infections*, 6th ed. Washington DC: American Public Health Association 1989:407–52.
36. Derogatis LR. *The SCL-90 Manual 1: scoring, administration, and procedure for the SCL-90*. Baltimore: Clinical Psychometrics Unit, John Hopkins University, 1977.
37. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
38. Robins LN, Helzer JE. *Diagnostic interview schedule version IIIA*. St Louis, Mo: Department of Psychiatry, Washington University School of Medicine, 1985.
39. *Diagnostic & statistical manual of mental disorders: DSM III-R*. Washington DC: American Psychiatric Association, 1987.
40. Wells VE, Klerman GL, Deykin EY. The prevalence of depressive symptoms in college students. *Soc Psychiatry* 1987;22:20–8.
41. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8–19.
42. Brawman-Mintzer O, Lydiard RB. Generalized anxiety disorder: issues in epidemiology. *J Clin Psychiatry* 1996;57(Suppl 7):3–8.
43. Brodsky AL, Heath CW. Infectious mononucleosis: epidemiologic patterns at United States colleges and universities. *Am J Epidemiol* 1972;96:87–93.
44. Heath CW, Brodsky AL, Potolsky AI. Infectious mononucleosis in a general population. *Am J Epidemiol* 1972;95:46–52.
45. Gelb D, West M, Zimmerman HJ. Serum enzymes in disease. IX. Analysis of factors responsible for elevated values in infectious mononucleosis. *Am J Med* 1962;33:249–61.
46. Aronson MD, Komaroff AL, Pass TM, Ervin CT, Branch WT. Heterophil antibody in adults with sore throat: frequency and clinical presentation. *Ann Intern Med* 1982;96:505–8.
47. Bender CE. Interpretation of hematologic and serologic findings in the diagnosis of infectious mononucleosis. *Ann Intern Med* 1958;49:852–65.
48. Carter RL. Platelet levels in infectious mononucleosis. *Blood* 1965;25:817–21.
49. Custer RP, Smith EB. The pathology of infectious mononucleosis. *Blood* 1948;3:830–57.
50. White PD, Thomas JM, Amess DH, et al. Incidence, risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever. *Br J Psychiatry* 1998;173:475–81.
51. Borysiewicz LK, Haworth SJ, Cohen J, Munding J, Rickinson A, Sissons JG. Epstein-Barr virus-specific immune defects in patients with persistent symptoms following infectious mononucleosis. *Q J Med* 1986; 58:111–21.
52. Sutton RN, Reynolds K, Almond JP, Marston SD,

- Emond RT. Immunoglobulins and EB virus antibodies in infectious mononucleosis. *Clin Exp Immunol* 1973;13:359–66.
53. Tobi M, Morag A, Ravid Z, et al. Prolonged atypical illness associated with serological evidence of persistent Epstein-Barr virus infection. *Lancet* 1982;1:61–4.
54. Reindenberg MM, Lowenthal DT. Adverse nondrug reactions. *N Engl J Med* 1968;279:678–9.
55. White PD, Grover SA, Kangro HO, Thomas JM, Amess J, Clare AW. The validity and reliability of the fatigue syndrome that follows glandular fever. *Psychol Med* 1995;25:917–24.