Chronic Illness Report 6:

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Epidemic (Chronic) Fatigue Syndrome:

Post-Viral Fatigue Syndrome (PVFS)

This report groups 101 important publications (**numbered)** into nine sections:

Selection of publications and editorial comments are by WH Murphy,

PhD, Professor Emeritus, Dept. of Microbiology and Immunology, University of Michigan School of Medicine.

Background

Bannister (1) notes that post-infectious syndromes have been recognized for the last five decades and that they may follow either bacterial or viral infections. His informative paper summarizes the evidence for and against a "post viral fatigue syndrome". The term 'post-viral fatigue syndrome' is preferred to 'chronic fatigue syndrome' because the latter has been confused with chronic or reactivated Epstein-Barr virus (EBV) infection. The Centers for Disease Control definition of the chronic fatigue syndrome (as "chronic disease syndrome") is presented by Holmes et al. (**2** below).

In keeping with its clinical characteristics, PVFS may be referred to as myalgic encephalomyelitis (ME), thus reflecting involvement of muscle tissue and the central nervous system. There is a consensus concerning the major signs and symptoms, as noted in the general reviews (**3**-**9**) below. The onset is sudden, with prodromal signs of a characteristic flu-like illness. PVFS is characterized by a chronic debilitating fatigue lasting six or more months. The fatigue is accompanied by fever, pharyngitis, myalgia, adenopathy, and arthralgias, although these signs occur variably. Psychiatric illnesses, such as depressive or anxiety disorders, occur in a significant number of patients with PVFS (see 7 below). These characteristics serve to distinguish PVFS as a clinical entity.

Pub.#:

1: Bannister, BA
1988
Post-infectious disease syndrome
Postgrad. Med. J. **64**: 559-567
Comment: This excellent review provides an accurate historical prospective of the PVFS. The disease, in its protean forms, has been recognized by physicians as a distinct clinical disease since the late 1950s.

2: Holmes, GP, JE Kaplan, NM Gantz, AL Komaroff, LB Schonberger, SE Straus, JF Jones, RE Dubois, C Cunningham-Rundles, S Pahwa, G Tosato, LS Zegans, DT Purtilo, N Brown, and RT Schooley
1988

Chronic fatigue syndrome: a working case definition
Annals Int. Med. **108**: 387-389
Comment: The article's abstract does not represent the substance of this valuable contribution, i.e., the authors' established benchmarks for an important "working case definition" for "the chronic fatigue syndrome". The *major criteria* consist of two parameters: (i) a definition of new-onset debilitating fatigue persisting for at least six months; and (ii) an exclusion of a large number (720) of other signs and symptoms. *Minor criteria* consist of two categories: (i) symptom criteria and (ii) physical criteria. A diagnosis must fulfill both major criteria and either (a) 6/11 symptom criteria and 2/3 physical criteria or (b) 8/11 symptom criteria. Specific laboratory tests or clinical measurements are not required to establish a diagnosis.

General Reviews

Pub.#:

3: Behan, PO and AM Bakheit
1991
Clinical spectrum of postviral fatigue syndrome
Brit. Med. Bull. **47**: 793-808
Comment: This excellent review discusses the limitations of the CDC and British Medical Council's definitions of the chronic fatigue syndrome. The authors outline approaches to making a reliable clinical diagnosis of PVFS and identify key criteria. Psychiatric disorders are evaluated; it is pointed out, for example, that depression in PVFS has distinctive qualities. The pathophysiology of PVFS is discussed, including abnormalities of the hypothalamus-pituitary axis that relate to severe night sweats, changes in body weight and appetite, fluid retention, fluctuations in body temperature, alterations in sleep pattern, and depression.

4: Byrne, E
1991
The chronic fatigue syndrome: a reappraisal and unifying hypothesis
Clin. Exp. Neurol. **28**: 128-138
Comment: This excellent review presents an important central concept, i.e., the "chronic fatigue syndrome" has a multifactorial basis. The concept is represented clearly by an appropriate Venn

diagram. An additional important contribution is that the author discusses fatigue and its causes in a nonpejorative manner. The review considers the appropriateness of various definitions of PVFS, putative viral causes, immunologic abnormalities, metabolic findings, neurophysiological studies, and psychiatric abnormalities. The discussions are clear, insightful, explicit, and informative.

5: Epstein, KR
1995
The chronically fatigued patient
Med. Clin. North Am. **79**: 315-327
Comment: This article illustrates that diagnostic evaluation, as well as the management of the patient presenting with chronic fatigue, can be done in an orderly manner.

6: Komaroff, AL and G Goldenberg
1989
The chronic fatigue syndrome: definition, current studies, and lesson for fibromyalgia research
*J. Rheumatol.***19** (Supple.): 23-27
Comment: This publication makes noteworthy contributions: (i) a good working definition of PVFS is provided and principal symptoms are summarized; (ii) PVFS and fibromyalgia are compared and contrasted; (iii) the frequency of important symptoms is documented; (iv) cognitive difficulties are enumerated and evaluated, (v) laboratory tests are listed and assessed, (vi) the putative role(s) of etiologic viruses are discussed, and (vii) the main results from a group of 350 patients with PVFS are presented in a very informative way. For example, average age was 37 years; 70% of patients were women; debilitating fatigue persisted for 2.9 years or longer; 25% of patients were bedridden and unable to work; and only 33% could work part-time.

7: Krupp, LB, WB Mendelson, and R Friedman
1991
An overview of chronic fatigue syndrome
J. Clin. Psy. **52**: 403-410
Comment: Krupp and his associates review "the chronic fatigue syndrome" from the viewpoint of the clinical psychiatrist. The review is comprehensive (86 papers), astute, objective, and insightful. For example, the critical appraisal of immunologic studies of the PVFS is unusal in depth and precision. Other contributions include the discussion of fatigue disorders in various diseases, psychiatric aspects of fatigue, sleep disorders in PVFS, and points of similarity between PVFS and fibromyalgia. Since PVFS and fibromyalgia share many common features, "it is not surprising that both conditions may coexist in the same individual." The section of

the review on diagnosis and treatment is a valuable contribution.

8: Moldofsky, H
1993
Fibromyalgia, sleep disorder and chronic fatigue syndrome
In Jenkins, R and JP Mowbray, eds. *Chronic fatigue syndrome. Ciba Foundation Symposium* **173**: 262-271
Comment: This publication, like Krupp et al. (**7**), compares the similarities and differences between PVFS and fibromyalgia.

9: Spracklen, FHN
1988
The chronic fatigue syndrome (myalgic encephalomyelitis)---myth or mystery.
S. African Med. J. **74**: 448-452
Comment: This contribution is robust, penetrating, insightful and refreshing. The author brings out many cogent observations: The incidence of PVFS in the UK approximates poliomyelitis prior to universal vaccination; myalgic encephalomyelitis (ME) is a clinically important disease; a member of the British Parliament introduced legislation aimed at confronting the disease; and environmental stress may be an important factor in the occurrence of ME. Spracklen also cites Dawsett's conclusion (Lancet **ii**:101, 1988) that the term "'chronic fatigue syndrome' does nothing to indicate the unique epidemiological, geographical, clinical and laboratory findings for ME. The use of the term would thus do nothing to reduce the confusion surrounding the diagnosis, therapy, and prognosis of the condition."

Epidemiologic Studies of the PVFS

Epidemiologic studies are confounded primarily by two important factors: (i) the failure of clinicians to recognize the PVFS as a clinical entity; and (ii) the lack of laboratory tests that confirm a clinical diagnosis of the disease. In a classic paper, Acheson (**10**) analyzed in detail (and with remarkable perception) 14 of the well-recognized epidemics. The paper by Koo (**22**) analyzes common defects in epidemiologic studies. The publication by Matthews et al. (**25**) is an example of excellently designed and executed epidemiological study. The contributions by Daugherty et al. (**11**) and Hill et al. (**12**) are examples of excellent and highly informative epidemiologic studies. The reports by Keighley and Bell (**14**) and Scott (**16**) establish that the astute clinician can readily diagnose PVFS as it

occurs either endemically or in its epidemic form. The fact that PVFS is a challenge to clinical diagnosis does not mean that it does not occur as a clinical entity or has some obscure basis.

Pub.#:

10: Acheson, ED
1959
The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland disease and epidemic neuromyasthenia
Am. J. Med. **26:** 569-595
Comment: This extraordinary review analyses 14 outbreaks of PVFS over the years 1934-1959. Endemic and epidemic occurrences are considered separately. Parameters are set forth that establish the PVFS as a distinct clinical entity. The author discusses with exemplary accuracy: epidemiologic and clinical features; laboratory findings; etiologic analyses; psychologic and psychiatric aspects; and appropriateness of nomenclature and terminology. An excellent discussion and summary are presented.

11: Daugherty, SA, BE Henry, DL Peterson, RL Swartz, S Bostien, and RS Thomas
1991
Chronic fatigue syndrome in northern Nevada
Rev. Infect. Dis. **13 (Suppl):** 39-44
Comment: This extremely well-controlled study, covering the period 1984-1988, involved *ca* 400 patients with clear-cut evidence for the PVFS. Two groups of patients (*ca* 20 each) were studied in detail and compared with age/sex-matched controls. The patients were not representative of the general population: average age 43; ratio of females to males 3:1; average income $75,000/yr. The neurologic and psychiatric evaluation of patients was particularly well done. MRI scans disclosed in most patients tiny punctate foci and multiple bilateral patchy areas in white matter tracts of the brain, accompanied by abnormal signal intensities, i.e., objective evidence for organic lesions in the brain. Personality disorders were analyzed relative to standard psychological tests: MMPI, Beck Depression Inventory, and Rahe Life Events Survey. The results showed that the protracted course of debilitating fatigue and accompanying behavioral abnormalities (over 35.5 months) were not attributable to elements of "hysterical" behavior.

12: Hill, RCJ, RWS Cheetham, and HL Wallace
1959
Epidemic myalgic encephalomyelopathy: the Durban outbreak

Lancet **i:** 689-693
Comment: This study of the summer outbreak of PVFS in the Addington Hospital (a training center for nurses) is excellent in every respect. Figures 1 and 2 of the report illustrate the suddeness of onset and age-distribution typical of the disease. The clinical phases of the disease are accurately analyzed; prodromal, acute, convalescent, and chronic phases. Physical and laboratory findings are presented clearly in appropriate tables. Psychiatric disturbances are described and assessed accurately. Possible roles of environmental toxins in the pathogenesis of the disease were considered and investigated. An accurate summary of the possible causes of the signs and symptoms characteristic of the disease is presented in a single short paragraph.

13: Jenkins, R
1991
Epidemiology: lessons from the past
Brit. Med. Bull. **47:** 952-965
Comment: As a baseline, Jenkins analyzed the classic early epidemics of PVFS and used this information to focus attention on the various factors that may contribute to the pathogenesis of the disease. The author's analysis of the psychiatric disorders that help distinguish the disease is very informative and dispels the misconception that "hysteria" is a factor in the origin of a diagnosis of PVFS. He notes, with some anguish, that in the UK the Surveillance Centre for Communicable Diseases does not record cases diagnosed as myalgic encephalomyelitis or PVFS. In an important contribution, Jenkins recommends that any analysis of the pathogenesis of PVFS should consider and evaluate its multifactorial basis.

14: Keighley, BD and EJ Bell
1983
Sporadic myalgic encephalomyelitis in a rural practice
.J. Royal College Gen. Pract. **33:** 339-341
Comment: This publication establishes two important points: (i) PVFS occurs endemically as sporadic cases. (ii) The astute clinician can diagnose the disease on a clinical basis without undue difficulty. See also Scott (**16**).

15: McEvedy, CP and AW Beard
1970
Concept of benign myalgic encephalomyelitis
Brit. Med. J. **1:** 11-15
Comment: This publication presents two basic notions: (i) During an incipient or ongoing poliomyelitis epidemic, presenting patients may misinform physicians (because of community hysteria) about

symptoms simulating poliomyelitis. (ii) Physicians in such communities, in response to the community hysteria, may inadvertantly overdiagnose clinical syndromes simulating poliomyelitis.

16: Scott, BD, JHE Baines, BPP Judge, and DG Mayne
1990
Epidemic malaise
Brit. Med. J. **i:** 170
Comment: These authors point out that good diagnosticians can readily identify benign myalgic encephalomyelitis in their patients, noting that hysteria plays no role in the process. They strongly disagree with the notions of McEvedy and Beard (**15**). This paper is one of many that disagree with the McEvedy-Beard notion that PVFS is mainly hysterical in origin.

17: Sigurdsson, B, M Gudnadottir, and G Petursson
1958
Response to poliomyelitis vaccination
Lancet **i:** 370-371
Comment: The authors raise two interesting points: (i) why the antibody response to Salk vaccine was poor in Egilsstadir but good in Thórshöln; and (ii) whether an antecedent epidemic of Akureyri fever in Thórshöln enhanced the antibody response to vaccine. These small but isolated communities are excellent subjects for epidemiologic studies in which environmental factors can be evaluated.

18: Wallace, PG
1991
Epidemiology: a critical review
Brit. Med. Bull. **47:** 943-951
Comment: A central theme in this review is the accurate clinical diagnosis of PVFS and how this is confounded by an inappropriate clinical definition of the disease. Wallace discusses estimates of the frequency of its occurrence among patients seen in general practice (280 / 10,000 subjects / year) and in hospitalized patients (3 to 5 / 100,000). The Myalgic Encephalomyelitis Association estimated *ca* 150,000 cases in the UK in their 1986 annual report. Such frequencies far exceed those for clinical poliomyelitis in virus-infected subjects prior to vaccination in temperate climates. The author notes the many flaws that occur in epidemiologic studies of PVFS and how various biases affect the analysis of data. The author is quite circumspect concerning the soundness of our knowledge of the PVFS.

EBV and HHV-6 as Putative Causes of PVFS

In clinical and seroepidemiological studies, a four-fold rise in serum antibody titer between *paired* acute and convalescent sera is considered to be necessary to establish an etiologic association between an infectious agent and a specific disease entity. In many epidemiologic studies, such a requirement is often difficult or impossible to meet. Koo (**22**) assessed a number of other weaknesses in epidemiologic studies carried out to determine whether EBV or HHV-6 infection was a major cause of the PVFS. The inherent problem is that both EBV and HHV-6 infect most humans during the first two decades of life. Thus, antibodies to their antigenic components are commonly found. Fluctuation of antibody titers is common. Subclinical persistent infections are known to be exacerbated by immunosuppressive experiences. From the publications listed below (**19, 21, 22, 25, 26**), it is evident that neither EBV nor HHV-6 are considered to be major causes of PVFS. The publication by Krueger and Sander (**24**) presents an excellent review of HHV-6 and its putative role(s) in various disease entities. The study by Bertram et al. (**20**) failed to implicate human cytomegalovirus in PVFS.

Pub.#:

19: Bagg, J
1991
Human herpesvirus-6: the latest human herpes virus
J. Oral Pathol. Med. **20:** 465-468

20: Bertram, G, N Dreiner, GR Krueger, A Ramon, DV Ablaski, SZ Salahuddin, and N Balachandram
1991
Frequent double infection with Epstein-Barr virus and human herpesvirus-6 in patients with acute infectious mononucleosis
In Vivo **5:** 271-279
Comment: Human cytomegalovirus (HCMV), like EBV and HHV-6, is a common cause of subclinical infections that can be activated in various ways, particularly in immunosuppressed subjects. This publication shows how difficult it is to ascribe an etiologic role to any of these viruses in various syndromes. The literature on PVFS tends to disregard HCMV as a putative etiologic agent of the disease.

21: Gold, D, R Bowden, J Sixbey, R Riggs, WJ Katon, R Ashley, RM

Obridgewitch, and L Carey
1991
Chronic fatigue: a prospective clinical and virologic study
JAMA **265:** 357-358
Comment: In a study comprising 26 patients with PVFS, these investigators did not find evidence of ongoing EBV infection in the test population.

22: Koo, D
1989
Chronic fatigue syndrome. A critical appraisal of the role of Epstein-Barr virus
West. J. Med. **150:** 590-596
Comment: Koo assessed seroepidemiologic studies carried out to evaluate whether EBV infection was a primary cause of PVFS. Koo makes a very valuable contribution in his analysis of both systemic and nonsystemic errors in such studies: (1) inaccurate clinical diagnoses; (2) poor selection of patients; (3) absence or lack of suitable controls; (4) inconsistencies in laboratory methodologies; etc. Koo does not accord significance to enterovirus infection in the pathogenesis of PVFS. Koo concludes that seroepidemiologic studies of EBV infection do not support a conclusion that EBV infection (acute, chronic or otherwise) is a primary cause of PVFS.

23: Krueger, GR, DV Ablaski, SF Josephs, SZ Salahuddin, U Lembke, A Ramon, and G Bertram
1991
Clinical indications and diagnostic techniques of human herpesvirus-6 (HHV-6) infection
In Vivo **5:** 287-295

24: Krueger, GR and C Sander
1989
What's new in human herpesvirus-6? Clinical immunopathology of the HHV-6 infection
Pathol. Res. Pract. **6:** 915-929

25: Matthews, DA, TJ Lane, and P Manu
1991
Antibodies to Epstein-Barr virus in patients with chronic fatigue
Southern Med. J. **84:** 832-839
Comments: This publication sets a standard for excellence in epidemiologic studies of the "chronic fatigue syndrome," both in the methodologies used and in the analysis of results. Patients with persistent chronic fatigue were divided accurately into two groups: those that had chronic EBV infection and those that did not.

Subjects were age- and sex-matched for prospective longitudinal studies. Detailed clinical and laboratory studies were done. Eight detailed tables of data are presented: (i) EBV serologic data; (ii) demographic and clinical characteristics; (iii) clinical features; (iv) symptomologies; (v) physical findings; (vi) laboratory findings; (vii) psychiatric evaluations; and (viii) attributable diagnoses. The data were carefully and critically evaluated and compared without bias to published findings that also are critically analyzed for both their strengths and weaknesses. Many important conclusions were reached. One conclusion, e.g., is that EBV serologic patterns have little clinical usefulness in evaluating patients with chronic fatigue. This conclusion has substance since it is in accord with conclusions reached in most similar investigations.

26: Sumaya, CV
1991
Serologic and virologic epidemiology of Epstein-Barr virus: relevance to chronic fatigue syndrome
Rev. Infect. Dis. **13 (Suppl.):** 19-25
Comment: Sumaya reviews the evidence indicating that EBV is not implicated in the pathogenesis of the PVFS. The difficulties in implicating EBV in either PVFS or multiple sclerosis are substantial, as noted in an analogous review by Sumaya and his coworkers (see CIR#8, pub.# **59**).

Enterovirus Infection and PVFS

This portion of the report consists of two subsections: **Enterovirus Sequences and Persistent Enterovirus Infection** (publication #s **27-42**) and **Enterovirus Sequences in Heart Disease** (#s **43-49**). The latter is included in order to document that enterovirus sequences (EVS) are commonly found in myocardial tissues. Because the subject of viral myocarditis is of major importance, it will be considered in detail in a subsequent report.

From the literature cited (**27-42**), it is evident that enteroviruses, particularly Coxsackieviruses, appear to play an important role in the pathogenesis of PVFS. The frequency of their occurrence in patients with PVFS was *ca* 35 to 67, as common (**36, 37**) as in controls. However, the actual frequency is difficult to assess and undoubtedly underestimated. For example, since the sampling of muscle tissues must be restricted (for practical reasons), it is not known which muscle groups contain EVS with the greatest frequency, and it is not known how stage or duration of disease affects frequency. There also are precautionary notes: the detection

of EVS in blood serum (**32**) indicates virus complexed with antibody; and the occurrence of EVS in buffy coat cells (**36**) cautions interpretations concerning detection of EBV in muscle biopsies. Thus, the direct detection of enterovirus-like particles in muscle biopsy by immune electron microscopy (**28**) is very important. The literature cited also documents that enteroviruses (particularly Coxsackieviruses) cause long-term persistent infections in which virus is detectable only by very sensitive PCR assays. The literature cited (**27, 34-38**) also makes it clear that the occurrence of elevated neutralizing antibodies, or IgM antibodies, is not a pathogenomic indicator for recent Coxsackievirus infection.

Evidence also was cited (**43-49**) documenting that enteroviruses, particularly members of the Coxsackievirus groups, persistently infect human cardiac tissues with end-stage disease (**48**), being dilated cardiomyopathy (CMP). Since CMP is the second most important cause of heart disease requiring cardiac transplants (ischemic heart disease is first), it is evident that additional information is sorely needed on the role of enterovirus infection as a predisposing factor in CMP. (The finding (**36**) that EVS are not uncommonly found in mammary or colon cancer tissues requires confirmation and further investigation.)

Enterovirus Sequences and Persistent Enterovirus Infection in PVFS

Pub.#:

27: Archard, LC, NE Bowles, PO Behan, EJ Bell, and D Doyle 1988
Postviral fatigue syndrome: persistence of enterovirus RNA in muscle and elevated creatine kinase
J. Royal Soc. Med. **81**: 326-329
Comment: By use of reverse-transcribed probes of conserved Coxsackie-B2 sequences and quantitative slot hybridization tests, assays were done on muscle biopsy specimens obtained from 96 patients that had diagnosed PVFS for as long as 20 years. Of these, 20 were positive and 76 negative for Coxsackie-B2 sequences. Since sampling of tissue was relatively minimal, the results undoubtedly underepresent the actual frequency of the occurrence of such sequences. Moreover, results undoubtedly were influenced by the severity of disease at the time when muscle biopsies were obtained. Other parameters of the PVFS were studied. In the sample of 20 patients, levels of creatine kinase tended to be elevated, i.e., evidence of muscle damage by single-fiber electromyographic (EMG) assays of muscle failed to consistently show abnormalities. Many of the patients had elevated levels of

serum IgG to Coxsackie-B2, but IgM levels were not consistently high. The authors suggest that PVFS is "a chronic metabolic myopathy induced by persistent virus infection."

28: Behan, PO, WMH Behan, JW Gow, H Cavanaugh, and S Gillespie
1993
Enterovirus and postviral fatigue syndrome
In Jenkins, R. and J. Mowbray (eds.), *Chronic fatigue syndrome. Ciba Foundation Symposium*, vol. 173, pp. 146-159. New York: J. Wiley & Sons
Comment: The Behans and Gow report important new findings. Solid-phase immunoelectron microscopy studies for the first time disclosed the presence of enterovirus-like particles in muscle biopsy specimens obtained from patients with the PVFS. An experimental model, with similarities to the PVFS, was established by infecting mice with Coxsackievirus B1, so that the acute and persistent phases of disease could be analyzed. Studies of the cytokine response during the acute phase of infection disclosed increased intracerebral levels of cytokines (evidently produced de novo in situ), including TNF-alpha. Increases of IL2, IL4, IL5, IL6, and IFN-gamma were not detected. By the use of PCR cytokine mapping, it was found that, in persistently infected mice, cytokines were upregulated in the brains. The continuous secretion of IL6 was of interest because of its putative role in causation of hypothalamic dysfunctions in persistently infected mice. While the reported findings need to be confirmed and extended, it is clear that they can provide important new insights into the pathophysiology of the PVFS.

29: Bell, EJ, RA McCarthy, and MH Riding
1988
Cocksackie B viruses and myalgic encephalomyelitis
J. Royal Soc. Med. **81**: 329-331
Comment: Two hundred ninety adults with diagnosed PVFS (1985-1986) were tested for IgM antibodies to Cocksackie viruses B, types 1-5. Thirty seven percent were positive compared to 9% of 500 adults free of PVFS. The authors suggest that such results "provide further evidence that Cocksackieviruses play a major role in ME, either directly or by triggering immunologic responses which result in abnormal muscle metabolism.

30: Bowles, NE, TA Bayston, H-Y Lhang, D Doyle, RJM Lane, L Cunningham, and LC Archard
1993
Persistence of enterovirus RNA in muscle biopsy samples suggests that some cases of chronic fatigue syndrome result from a previous, inflammatory viral myopathy

J. Med. **24**: 145-160
Comment: These investigators used a Coxsackievirus B2 probe to detect homologous sequences in five groups of subjects: (1) patients with adult dermatomyositis (DM); (2) those with juvenile dermatomyositis (JDM); (3) patients with polymyositis (PM); (4) those with PVFS; and (5) controls. It is not clear that subjects were age- or sex-matched; controls were not fully described. The frequency of the occurrence of viral sequences in groups 1-3 and patients with PVFS were essentially identical. Where strand-specific probes were used for assays on PVFS patients, equivalent amounts of genomic and template strands were found, i.e., so-called symmetric RNA syntheses indicative of defective virus replication. The authors make two very cogent suggestions: (1) symmetric viral RNA syntheses result in the production of defective virus that is not eliminated immunologically; and (2) cardiomyopathy in groups 1-3 may be a sequel to persistent defective virus infection. The high frequency of viral sequences in the control group of subjects has many important implications.

31: Cao, Y and DP Schnurr
1988
Persistent infection of YAC-1 cells by Coxsackievirus B3
J. Gen. Virol. **69**: 59-65.

32: Clements, GB, F McGarry, C Nairn, and DN Galbraith
1995
Detection of enterovirus-specific RNA in serum: the relationship to chronic fatigue
J. Med. Virol. **45:** 156-161.
Comment: In this excellent study, three groups were tested: 118 patients with PVFS; 110 hospitalized patients experiencing enterovirus infection that was not PVFS; and 126 healthy subjects. For the most part, subjects were age- and sex-matched. Enterovirus sequences ("nested PCR assays") were found in 36/88 serum samples from the first group, in 22/82 of the second, and in 3/126 of the third. The first group appeared to have higher amounts of sequences. The authors make numerous significant observations. For example: The skewed sex distribution among PVFS patients disappears in subjects with the syndrome in excess of 2 years; that enterovirus infection in their population had a rather stable incidence of *ca* 1-2% that was not seasonal; and that, in a population of 106 subjects seen by general practitioners, there was a frequency of PVFS of *ca* 0.1% (1154 cases).

33: Cunningham, L, NE Bowles, RJ Lane, V Dubowitz, and LC Archard
1990

Persistence of enteroviral RNA in chronic fatigue syndrome is associated with the abnormal production of equal amounts of positive and negative strands of enteroviral RNA
J. Gen. Virol. **71**: 1399-1402.
Comment: Using Coxsackievirus B2 as a model, probes were used that were specific for either genomic (+ stranded) or template (- stranded) viral RNA. In productively infected cells in vitro, *genomic* viral RNA was found at 100-fold excess compared to *template* RNA, i.e., so-called asymmetric synthesis. In muscle biopsy specimens obtained from patients with PVFS, both classes of RNA were found in equal amounts, i.e., such cells presumably were infected with "defective" virus that had the capacity to establish persistent infection. However, these important findings can be interpreted in a number of other ways.

34: Cunningham, L, NE Bowles, and LC Archard
1991
Persistent virus infection of muscle in postviral fatigue syndrome
Brit. Med. Bull. **47**: 852-871
Editorial comment: Cunningham and his associates determined whether enterovirus sequences were present in muscle biopsy specimens obtained from patients with PVFS. Two classes of probes were used: (i) so-called generic probes that were enterovirus group-specific; and (ii) probes that made it possible to determine whether virus RNA synthesis was asymmetrical (typical of cytic infection) or symmetrical (typical of "defective" viral RNA synthesis). Importantly, appropriate probes were used to test whether specimens also were positive for EBV sequences. Seventeen patients were studied that had fatigue for six or more months. Of these, five were mates and 13/17 were at midlife, i.e., 35-55 years of age. Then patients were tested for neutralizing antibody to Coxsackievirus B3; five were negative. Eleven patients were tested for IgM to Coxsackievirus B2, 3 and 5; of these, 10 were negative. Such results indicate that antibodies to Coxsackieviruses are not good surrogate markers for PVFS. When muscle biopsy specimens from 140 PVFS patients were tested for enterovirus sequences, 34 were positive (24%). All of 152 controls were negative. Seventy-six patient specimens were tested for EBV-specific sequences. Only eight were positive, thus contraindicating a significant role for EBV in the pathogenesis of the PVFS. All of the specimens positive for enterovirus sequences provided evidence for symmetrical syntheses of enterovirus RNA. The authors interpret this to mean that such results are evidence for persistent defective virus infection. However, no "defective virus mutants" were isolated and the term "mutant" was not used rigorously.

35: Dawson, J
1987
Royal free disease: perplexity continues
Brit. Med. J. **294**: 327-328.
Comment: Outside of the US, a strong consensus exists that Coxsackievirus infection appears to play a major role in the pathogenesis of PVFS. Commonly, it was believed that IgM antibodies to Coxsackie viruses were a reliable indicator of recent infection. Dawson comments that when IgM serologic studies were done in PVFS patients and appropriate controls, the results indicated an equivalent level of exposure in PVFS patients and controls. This led to the suggestion by one of the investigators (Dr. H. A. Carmichael, vale of Leven Hospital) that "another unknown factor acting against the background of a high degree of exposure to Coxsackie B virus" might be involved.

36: Gow, JW and WMH Behan
1991
Amplification and identification of enteroviral sequences in the postviral fatigue syndrome
Brit. Med. Bull. **47**: 872-885
Comment: Many important points are brought out by Gow and Behan: (1) The probes used to detect enterovirus sequences (EVS) detect most but not all enteroviruses. (2) Antibody titers to enteroviruses in PVFS and control patients did not differ significantly. (3) EVS were 6.7 times more frequent in PVFS patients than in controls. (4) Elevated levels of creatine kinase are not always found in PVFS patients. (5) Possibly HTLV-I or HTLV-II sequences were detected in buffy coat specimens obtained from PVFS patients. Interestingly, in the control group EVS were detected in 5/12 patients with mammary cancer and in 1/3 with carcinoma of the colon. Similarly, the detection of EVS in buffy coat specimens in both test and control groups has many interesting implications. From their studies, the authors estimate an equivalent of 1 enterovirus virion / 2000 cells. The authors discuss how such a frequency may impinge on the detection of EVS in biopsy specimens obtained from various muscle groups. Possible seasonal impacts, or prior exposure to prophylactic enterovirus vaccine, was not discussed.

37: Gow, JW, WMH Behan, GB Clements, C Woodall, M Riding, and PO Behan
1991
Enteroviral RNA sequences detected by polymerase chain reaction in muscle of patients with postviral fatigue syndrome
Brit. J. Med. **302**: 692-696

Comment: Antibody and enterovirus sequence assays were done in 60 patients with PVFS and 41 controls. Overall, RNA sequences were detected in skeletal muscle biopsy specimens of 53% of the PVFS group compared to 15% for controls. Interestingly, and as noted by Tracy et al. (**49**), the occurrence of such sequences did not correlate with elevated antibody levels to Coxsackie viruses B1-B5.

38: Matteucci, D, M Pagliante, AM Giangregorio, MR Copobianchi, F Dianzani, and M Bendinelli
1982
Group B Coxsackieviruses readily establish persistent infections in human lymphoid cell lines
J. Virol. **56:** 651-654.
Comment: Because Coxsackieviruses cause a variety of immunologic abnormalities, the described model provides a methodology to analyze the interactions between Coxsackievirus mutants possessing different pathogenic capabilities and subpopulations of human lymphoid cells. The bibliography lists major papers on persistent viral infection and on defective interfering viruses.

39: Righthand, VF and RV Blackburn
1989
Steady-state infection by ECHOvirus 6 associated with nonlytic viral RNA and an unprocessed capsid polypeptide
J. Virol. **63**: 5268-5275
Comment: The in vitro model of Echovirus 6 persistently-infected human cells is an excellent paradigm for analyzing mechanisms of persistent defective enterovirus infection. The introduction of the paper describes the extraordinary features of the model. They include: noncytopathic infection; production of virions in the same quantitative amounts as corresponding lytic virus; and that persistent infection was not dependent on exogenous antiviral antibody or interferon. The authors suggest that "the viral RNA is transferred to daughter cells during division." The episomal transfer of enterovirus RNA genomes is not a common phenomenon.

40: Strongwater, SL, K Dorovini-Zis, RD Ball, and TJ Schnitzer
1984
A murine model of polymyositis induced by Coxsackievirus B1 (Tucson strain)
Arthritis Rheum. **27**: 433-442
Comment: This publication is representative of a very large literature in which various Coxsackievirus types were used (mostly the B subgroup) to establish persistent infections in mice and where "autoimmune" mechanisms appear to be a major cause of cardiac

myocarditis. In such studies, results can be influenced markedly by the types of virus "mutant" used and the strain of mice employed.

41: Woodall, CJ, MH Riding, DI Graham, and GB Clements
1994
Sequences specific for enteroviruses detected in spinal cord from patients with motor neuronic disease
Brit. Med. J. **308:** 1541-1543.
Comment: These authors report that their PCR assays detected enterovirus sequences in 8/11 patients with motor neuron disease (MND) but not in six age- and sex-matched controls. Poliovirus-infected monkeys used as positive controls also were positive. The sequences detected in MND patients were homologous to those of Coxsackie B5 and appeared to comprise two subgroups. The authors conclude that there was low level persistent enterovirus infection in cord tissues of MND patients that was not detectable by conventional virus isolation techniques. They suggest a state of restricted enterovirus replication in cord tissue analogous to the restricted replication of measles virus in subacute sclerosing panencephalitis.

42: Zoll, GJ, WJG Melchers, H Kopecka, G Jambroes, HJA van der Poll, and JMD Galama
1992
General primer-mediated polymerase chain reaction for detection of enteroviruses: application for diagnostic routine and persistent infections
J Clin. Microbiol. **30**: 160-165
Comment: The importance of the types of primers used to generate enterovirus probes for PCR assays for EVS is explicitly considered in this valuable paper. The authors report that their "generic enterovirus probes" did not amplify Coxsackievirus A11, A17 or A24 sequences, or those of ECHO viruses 16, 22, and 23. Other investigators have also reported that such generic probes may not amplify some Coxsackievirus A types. Moreover, based on PCR studies, ECHO 9 is in fact a Coxsackievirus. Statements in the literature that "generic enterovirus probes detect *all* enteroviruses" lack precision. Additionally, there is little published data on how probes constructed to detect different segments of enterovirus genomes detect corresponding sequences in various test samples.

Enterovirus Sequences in Heart Tissues

Pub.#:

43: Archard, LC, NE Bowles, L Cunningham, CA Freeke, EG Olsen, ML Rose, B Meany, HJ Why, and PJ Richardson

1991
Molecular probes for detection of persisting enterovirus infection of human heart and their prognostic value
Eur. Heart J. **12** (Suppl.): 56-59.
Comment: This paper stresses the importance of antecedent or persistent defective enterovirus infection in the pathogenesis of the inflammatory cardiomyopathies. It is proposed that such infections progress to end-stage disease requiring cardiac transplant. Better methods are needed to detect such viruses, since standard virus isolation techniques and immunologic assays for relevant enterovirus antigens are usually negative. The authors note that "persisting enterovisus RNA in dilated cardiomyopathy is the strongest known predictor of poor prognosis."

44: Bowles, NE, PJ Richardson, EGJ Olsen, and LC Archard
1986
Detection of Coxsackie-B-virus-specific RNA sequences in biopsy samples from patients with myocarditis and dilated cardiomyopathy
Lancet **i:**1120-1123
Comment: DNA complementary to 6.3-kb of the Coxsackie B-2 genome was synthesized by reverse transcription. A 1.6-kb segment homologous to the conserved 3 ' region of the viral genome was used to detect Coxsackie B-2 sequences (CB2) in myocardial samples obtained from patients with either active or healing myocarditis or patients with dilated cardiomyopathy exhibiting inflammatory changes. In tests on 17 patients, nine were positive. Only four patients putatively free of Coxsackie virus infection were tested. All were negative. Several interesting observations were made: CB2 sequences were detected "in a large proportion of patients diagnosed as having active or healed myocarditis or congestive cardiomyopathy ensuing from this disorder"; in positive samples, virus RNA was present "at between 10 and 100 copies per cell equivalent." The latter results suggest persistent infection even in the convalescent patient. The authors make the important suggestion that the failure to detect such viruses or their antigens by conventional assays might have resulted from incorrect post-translational processing of viral capsid precursor or immunologtic masking by antibody.

45: Jehn, VW and MK Fink
1980
Myositis, myoglobinemia, and myoglobinemia associated with enterovirus ECHO 9 infection
Arch. Neurol. **37**: 457-458
Comment: The findings summarized by Jehn and Fink serve the purpose of suggesting that the pathogenesis of viral myocarditis

may not be restricted to the Coxsackievirus families.

46: Muir, P, AJ Tilzey, TAH English, F Nicholson, M Signy, and JE Banatvala
1989
Chronic relapsing pericarditis and dilated cardiomyopathy: serologic evidence of persistent enterovirus infection
Lancet **i:** 804-807.
Comment: The authors' findings are consistent with the notion that persistent enterovirus infection is associated with chronic pericarditis and dilated cardiomyopathy, i.e, the data reported indicate that patients with chronic relapsing pericarditis experience persistent antigenic stimulation, predominately by Coxsackie B viruses. The authors suggest the possibility that virus may persist at extracardiac sites. Occurrence of disease was noted to be linked to some HLA allotypes, thus suggesting a genetic predisposition. The authors comment that enteroviruses appear to be a common cause of some chronic cardiac diseases. They note that after ischemic heart disease, dilated cardiomyopathy is the most common reason for cardiac transplantation in the UK. The authors also observe that improved diagnostic methods should lead to a better understanding of the pathogenesis of virus-induced cardiac disease and its prevention.

47: Schwaiger, A, F Umlauft, K Weyrer, C Larcher, J Lyons, V Mühlberger, O Dietze, and K Grünewald
1993
Detection of enteroviral ribonucleic acid in myocardial biopsies from patients with idiopathic dilated cardiomyopathy by polymerase chain reaction
*Am. Heart J.***126**: 406-410
Comment: Nineteen patients with idiopathic dilated cardiomyopathy (CMP), along with appropriate controls, were tested for enterovirus sequences in heart muscle biopsy specimens. Two probes were used for PCR assays: one specific for Coxsackie B3 (CV-B3) and the other for enteroviruses in general. None of the controls yielded positive results. Since only 1/19 patients with heart disease was positive for CV-B3 sequences, while 5/16 were otherwise positive, the authors suggest that enteroviruses other than CV-B3 may be implicated in CMP.

48: Tang, TT, GV Sedmark, KA Siegsmund, and SR McCreadie
1975
Chronic myopathy associated with Coxsackievirus type A9: a combined electron microscopy and viral isolation study
N. Engl. J. Med. **292**: 608-611.
Comment: This paper simply establishes that members of the

Coxsackievirus A group also can cause chronic myopathy.

49: Tracy, S, NM Chapman, BM McManus, MA Pallansch, MA Beck, and J Carstens
1990
A molecular and serologic evaluation of enteroviral involvement in human myocarditis
J. Molec. Cell. Cardiol. **22**: 403-414.
Comment: This publication makes several important observations: (1) No hybridization probe used as of the publication date detected a specific enterovirus group to the exclusion of all others; and (2) when a "generic enterovirus probe" was used to detect enterovirus sequences in human myocardial specimens and the results then compared to IgM antibody titers, the authors could not make a correlation between the two. There are many reasons why this may have happened. In any case, the frequency of the occurrence of enterovirus sequences in human muscle tissue, of vaccine origin or otherwise, in the general population is unknown, and disease associations are not clearly evident.

Retroviruses as Putative Etiologic Agents in PVFS

Only three publications were found, two of them preliminary and none peer-reviewed, that provide laboratory evidence for a possible role of human retroviruses in the etiology of PVFS. The problem is not in detecting such agents, but in implicating detected agents in the syndrome, i.e., any hypotheses about their etiologic role must be reconciled with pathogenesis, epidemiologic data, and geographic distribution. There is an abundance of evidence documenting that exogenous or endogenous retroviruses can be found in human cells or tissues (see Urnovitz and Murphy, *Clin. Microbiol. Rev.* **9:** 72-99: 1996). But implicating them as etiologic agents of specific disease entities is a difficult problem.

Pub.#:

50: DeFreitas, E, B Hilliard, PR Cheney, DS Bell, E Kiggundu, D Sankey, Z Wroblewska, M Palladino, JP Woodward, and H Koprowski
1991
Retrovirus sequences related to human T-lymphocyte virus type II in patients with chronic fatigue immune dysfunction syndrome
Proc. Natl. Acad. Sci. USA **88:** 2922-2926
Comment: The studies reported by DeFreitas et al. were well-

designed and appear to have been well-executed. The subjects were: 12 adults with diagnosed PVFS from the greater N. Carolina region and19 pediatric patients drawn from a local epidemic of PVFS in upstate rural New York. Controls consisted of 20 subjects not exposed to PVFS patients. Fifty percent of the adults and 61% of the pediatric patients had antibodies to HTLV *gag* and *env* products. Controls were all negative. When peripheral blood leukocytes from PVFS patients were tested by PCR for *gag* and *tax* sequences of HTLV-I, they were all negative. However, when subjects with PVFS were tested for HTLV-II *gag* and *env* sequences, 83% of adults and 72% of pediatric specimens were positive. Moreover, *gag* gene expression was positive in 7/10 HTLV-II *gag*-positive specimens, as demonstrated by *gag*-gene-directed RNA synthesis. The authors comment that they did not believe that they had detected activated endogenous retrovirus sequences. For unknown reasons, other investigators did not confirm the described results; but this does not mean that they were not accurate. For example, Banki et al., *Proc. Natl. Sci.* **89:** 1939 (1982), reported that HERV HRES-1 encoded a protein possibly acting as an autoantigen for HTLV-1 *gag*-reactive autoantibodies.

51: Folks, TM, W Heneine, A Khan, T Woods, L Chapman, and L Schonberger
1993
Investigation of retroviral involvement in chronic fatigue syndrome
In R Jenkins and J Mowbray, eds. *Chronic fatigue syndrome. Ciba Foundation Symposium* **173:** 160-166. New York: J. Wiley & Sons
Comment: Four groups of subjects were studied as part of the CDC surveillance program for the chronic fatigue syndrome (CFS). Group I was diagnosed CFS. Group II: patients with disease approximating CFS. Groups III and IV: patients with predisposing diseases that could approximate CFS. Two sets of primer / probes were used, one for HTLV-II 5 ' *gag* sequences; the other for *tax* sequences. PCR assays were done using the "whole blood lysate method". None of 26 test or 28 control subjects were positive for the probes used. Results also were negative where tests were done for other retrovirus sequences: bovine leukemia virus; simian retrovirus types 1, 2 and 3; simian T-cell leukemia virus; and "human spumavirus".

52: Holmes, MJ
1992
A retrovirus etiology for CFS
In BM Hyde et al., eds. *The clinical and scientific basis of myalgic encephalomyelitis chronic fatigue syndrome.* Ottawa: Nightingale Research Foundation

Comment: In this preliminary study, experiments were carried out on six patients with diagnosed PVFS and six age- and sex-matched controls. Lymphocyte cultures established from peripheral blood specimens were tested for reverse transcriptase (RT) activity and examined by thin-section electron microscopy. The RT activity of cells obtained from the PVFS patients was from 1.5 to 4 times as high as that found in control cells. The author noted that the mitogen preparation used to sitmulate lymphocyte cultures contained a "powerful inhibitor" of RT activity. Nevertheless, the author did not regard the RT results to be "decisive". The six electron micrographs in the publication convincingly show the presence of multiple budding C-type virus particles with the structural characteristics of retroviruses.

53: Jubelt, B
1992
Motor neuron diseases and viruses: poliovirus, retrovirus and lymphomas
Curr. Opin. Neurol. Neurosurg. **5:** 655-658
Comment: This excellent review illustrates the difficulties inherent in adducing convincing evidence that either a known or previously undetected human retrovirus may be implicated etiologically in a given clinical entity. The examples used are antecendent poliovirus or HTLV-I or HTLV-II in the pathogenesis of human motor neuron disease. To implicate a human retrovirus in the etiology of the PVFS is a more difficult challenge.

Immunologic Aspects of PVFS

The publications listed in this section comprise mainly two categories: general reviews and publications on viruses as causes of immunologic abnormalities in PVFS. Because of the putative importance of enterovirus infections in the pathogenesis of PVFS, immunologic abnormalities attributable to Coxsackievirus infections are emphasized. Surprisingly, rather limited information was found in three key areas: genetics of susceptibility, allergic phenomena that may predispose to PVFS, and the role(s) of the various cytokines on the pathogenesis of PVFS. Comprehensive reviews addressing these subjects explicitly and in detail were not found. The most extensive collection of reviews on immunologic aspects of PVFS are published in BM Hyde et al., eds. *The clinical and scientific basis of myalgic encephalomyelitis chronic fatigue syndrome* (Ontario, Canada: Nightingale Research Foundation, 1992). The section devoted to immunologic studies of PVFS consists of four

chapters, for a total of 45 pages. Two additional chapters deal with immune-based therapeutic approaches.

Featured Reviews

Pub.#:

54: Conaldi, PG, D Matteucci, SM Guidi, and M Bendinelli
1988
Interaction of group B Coxsackieviruses with immunocytes
In HP Schulteiss, ed. *New concepts in viral heart disease: virology, immunology, clinical management.* New York: Springer-Verlag: 195-204
Comment: The authors' theme is that type B Coxsackieviruses alter immune functions in vivo and cause a "profound involution of both central and peripheral lymphoid organs." The striking depletion of lymphoid cells in the thymus, spleen and lymph nodes occurred without direct cytopathic viral effects, since virus replication in such cells was not detectable. Thus, the important causes for such effects remain unknown. In Coxsackievirus-B3-infected mice, the thymus is affected first. Effects are so substantial that the organ's architectural features become obscured. Lymphocyte depletion in the spleen and lymph nodes involves both the T- and B-cell areas. In humans, Coxsackievirus infection reportedly caused a 20-50% reduction in the peripheral blood mononuclear cell lymphocyte response to mitogens and was neither age- nor gender-related. Coxsackieviruses readily cause persistent infections of human lymphoid cell lines, or either B or T cell origin. Antibody frees cultures of persistent infection.

55: Garzelli, C, F Basolo, D Matteucci, BS Prabhakar, and A Toniolo
1988
Picornavirus-induced immunosuppression
In S Specter et al., eds. *Virus-induced immunosuppression.* New York: Plenum: 217-234
Comment: On the whole, this review indicates the importance of enterovirus infection on the lymphoid system and the consequent immunologic abnormalities. The authors point out that polioviruses replicate in blood monocytes and in established human lymphoid cell lines, and that polioviruses can establish persistent infections in cell lines of either B- or T-cell origin. Some of the ECHO viruses alter the surface properties of human polymorphonuclear cells. The basic features of the experimental model of Coxsackievirus-B3-infected mice is described. In persistently infected mice, cell-mediated immunity in vivo and the T-cell-dependent response in vitro are impaired. The authors ascribe the immunodeficiencies observed in persistently-infected mice to two main causes: damage

to antigen-presenting cells and activation of suppressor T-cells. The authors propose that a progressive loss of lymphocytes in infected mice accompanies the development of autoreactivity which contributes to virus-induced immunodeficiency. But the results summarized do not signify that losses of lymphoid cells in the thymus, spleen or lymph nodes were a direct consequence of virus cytopathology. Sixty-one well-selected references are listed in the bibliography.

56: Gin, W, FT Christianson, and JB Peter
1989
Immune function and the chronic fatigue syndrome
Med. J. Australia **151:** 117-118
Comment: The authors note that immunologic studies of PVFS are confounded by variability which they attribute to three main factors: (i) The protean nature of the disease; (ii) stage of disease when patients are studied; and (iii) technologic differences among the immunologic tests applied. Overall, results from 124 PVFS patients were summarized. The consistent results were as follows: (1) a decreased absolute number of peripheral blood CD4 and CD8 cells; (2) a decreased lymphocyte response to mitogens; (3) a decreased response in delayed hypersensitivity tests; (4) a decreased NK cell response; and (5) sometimes a deficiency in the IgG1 immunoglobulin subclass. The authors comment that the severity of the abnormalities are often striking. They also noted an increased expression of the HLA-DR histocompatibility antigen in peripheral blood monocytes, an event that, paradoxically, is suggestive of immune activation.

Contemporary Reviews

Pub.#:

57: Buchwald, D and AL Komaroff
1991
Review of laboratory findings for patients with chronic fatigue syndrome
Rev. Infect. Dis. **13 (Suppl):** 12-18
Comment: This report summarizes a substantial and valuable effort designed to analyze immunologic abnormalities in patients with PVFS. The authors identified major confounding factors in such an analysis that inherently limit the accuracy of their analysis: (i) patient heterogeneity, (ii) differences in test methods, (iii) failure to standardize test parameters, (iv) differences in stage of disease, and (v) lack of age- or sex-matched controls. The major immunologic parameters reviewed in the analysis include: hematology, serum chemistry, autoantibody levels, qualities and

classes of immunoglobulins in serum, immune complexes, cytokines, T-cell subsets and functional activities, phenotype and functional activities of NK cells, phenotype and functional activities of B cells, and predisposition to allergic reactivities. Thus, it is not clear how the results relate to PVFS, since PVFS is a distinct clinical entity not to be confused with chronic EBV infection. Nonetheless, this publication is a valuable contribution, since it attempts to make sense of a large and inconsistent literature. Sixty-one well-selected references are listed in the bibliography.

58: Prieto, J, J Camps-Bansell, and A Castilla
1993
Opiod-mediated monocyte dysfunction in the chronic fatigue syndrome
In BM Hyde et al., eds. *The clinical and scientific basis for myalgic encephalomyelitis chronic fatigue syndrome.* Ottawa: Nightingale Research Foundation: 575-584
Comment: This article focuses on the stress axis and how it interacts with the immune system. The authors suggest that their findings indicate increased opoid activity, such as the enkephalins, in patients with PVFS and that they are associated with various immunologic abnormalities. Figure 1 diagrams the stress axis; figure 6 diagrams type A and type B stress responses. This publication summarizes many of the elements of psychoneuroimmunology. Eighty-three key publications are cited.

59: Pross, HF
1993
Abnormalities of natural killer (NK) cell numbers and function in patients with chronic fatigue immune dysfunction syndrome (CFIDS)
In BM Hyde et al., eds. *The clinical and scientific basis for myalgic encephalomyelitis chronic fatigue syndrome.* Ottawa: Nightingale Research Foundation: 566-572
Comment: The author provides an excellent and clear summary of the immunologic abnormalities that may be found in patients with PVFS. He comments that the lack of suitable diagnostic tests, as an aide in the diagnosis of PVFS, contributes to the inconsistencies found in reports of immunologic studies of the PVFS. The author also notes that the literature on NK studies is confounded by the use of the 'NK' designation to mean either CD3+ or CD3- non-MHC lysis of target cells (usually K562 cells) and equating the CD56 phenotype with NK-mediated target cell lysis. Nonetheless, the author draws three main conclusions. In patients with PVFS, (1) NK activity is significantly lower than controls; (2) total CD56+ cells are increased; and (3) the proportion of CD3-CD56+ cells is decreased. Forty nine well-selected publications are listed in the bibliography.

60: Rouse, BT and DW Horohov
1986
Immunosuppression in viral infections
Rev. Infec. Dis. **8:** 850-873
Comment: This contribution is a major review on viral-induced immunosuppression. Its abstract does not convey the substance of the article's contribution. The article excells in clarity as well as in depth. The bibliography lists 222 references. Organization is excellent. The tables provide important explicit information that is thoroughly referenced. Throughout, the authors clearly present the basic conceptual foundations important to understanding how the various mechanisms operative in viral-induced immunosuppression act in a functional way.

Featured Publications

The papers listed below are selected to emphasize specific points. For example, Behan et al. (**61**), Gupta et al. (**64**), and Lloyd et al. (**65**) are reasonably consistent in reporting the immunologic abnormalities that occur in patients with PVFS. Careful patient selection was the key point, i.e., patients with active or chronic EBV infection were excluded for the most part. The reports by Bendinelli et al (**62**) and Metteucci et al. (**67**) document that enterovirus infections in mice cause severe immunologic abnormalities and atrophy of lymphoid tissues not attributable to viral replication. Coxsackie B viruses readily cause persistent noncytopathic infections of human lymphoid cells in vitro (**66**). The report by Caligiuri (**63**) is representative of many that consistently show depressed NK cell function in PVFS patients. Lloyd et al. (**65**) convincingly document that IgG1 and IgG3 levels, and delayed hypersensitivity reactivities, were depressed in patients with PVFS (in 56/100 and 88/100 patients, respectively). Peterson et al. (**75**) and Read et al. (**77**) report similar results. The purported variability in immunologic abnormalities in patients with PVFS appears to be overstated and may reflect, instead, inappropriate patient selection, principally by investigators in the U.S.

Pub.#:

61: Behan, PO, WMH Behan, and EJ Bell
1985
The postviral fatigue syndrome - an analysis of the findings in 50 cases
J. Infect. **10:** 211-222
Comment: In-depth studies were done on 50 patients at both acute and chronic stages of disease. Extensive clinical laboratory

tests were done, including single-fiber electromyographic (EMG) and nuclear magnetic resonance (NMR) studies of muscle. In a test group of 20 patients, scattered necrotic muscle fibers were found without evidence of inflammatory infiltrates. The NMR tests disclosed abnormal muscle metabolism that was characterized by excessive intracellular acidosis. Acute disease was characterized by an absolute decrease in T4 and T8 cells. In acute disease there was a significant decrease in T8 cells, while T4 cells were decreased in chronic disease. There was an impaired lymphoproliferative response to phytohemagglutinin. Eighteen patients had high serum antibody titers to smooth muscle. Serologic studies disclosed that 70% of patients had high titers to Coxsackie B viruses. On the whole, other immunlogic abnormalities were not found. The authors suggest that PVFS results from "the interaction of viral infection and immunologic processes which produce damage to intracellular enzymes and result in abnormal muscle metabolism, especially on exercise."

62: Bendinelli, M, D Matteucci, A Toniolo, AM Patone, and MP Pistillo
1982
Impairment of immunocompetent mouse spleen cell functions by infection with Coxsackievirus B3
J. Infect. Dis. **146:** 797-805
Comment: This important study analyzed the effects of the infection of BALB/c inbred mice with Coxsackievirus B3. The antibody response to sheep red blood cells was reduced, an effect not attributable to losses in B-cell functions. Immune suppression was attributed to loss in macrophage functions, presumably at the level of antigen presentation, and in combination with nonspecific T-cell suppression. Marked atrophy of the spleen occurred in infected mice and presumably affected B-cell and T-cell regions equally. There was no significant evidence that virus multiplied or was cytopathic to splenocytes. The possible suppression of monocyte function in humans as a result of poliovirus infection was discussed, using the described experimental model as a paradigm. The bibliography lists 36 references.

63: Caligiuri, M, C Murray, D Buchwald, H Levine, P Cheney, D Peterson, AL Komaroff, and J Ritz
1987
Phenotypic and function deficiency of natural killer cells in patients with chronic fatigue syndrome
J. Immunol. **139:** 3306-3313
Comments: Although the results in the described study were resaonsably consistent, the diagnoses of PVFS in the patients selected was somewhat discrepant. Nonetheless, this paper is representative of many reporting the repression of NK functions in

patients with PVFS.

64: Gupta, S and B Vayuvegula
1991
A comprehensive immunological analysis in chronic fatigue syndrome
Scand. J. Immunol. **33:** 319-327
Comments: The authors studied 20 CDC-defined patients with PVFS, along with age- and sex-matched controls. The main findings suggest immunological dysfunction in patients with CFS. In particular, studies of the adhesion molecule LFA-1 and its ligand ICAM-1 revealed an increased proportion of CD4+ ICAM-1+ T-cells. Blood monocytes also showed increased densities of surface LFA and ICAM. The antibody response to type 3 pneumococcal antigen was impaired in PVFS, while the response to types 8, 12, and 14 evidently was not. Studies of serum autoantibodies disclosed that 30% of patients with PVFS had elevated titers only to ANA. On the whole, the authors provide a perceptive and well-balanced assessment of their findings and how they relate to similar published findings. It is gratifying to note that they discriminate PVFS as a clinical entity and do not confuse it with chronic EBV infection.

65: Lloyd, AR, D Wakefield, CR Boughton, and JM Dwyer
1989
Immunologic abnormalities in the chronic fatigue syndrome
Med. J. Australia **151:** 122-124
Comment: This study was carried out on a carefully defined group of patients that had experienced long-standing disease (mean: 37 mos.). Controls were matched carefully by age and sex. Absolute numbers of peripheral blood T-cells were determined, not ratios. Delayed hypersensitivity (DTH) responses were determined by the Multitest CMI System. Serum immunoglobulin subclasses also were quantified. The authors report an absolute reduction in helper / inducer T-cells (CD2, CD4) and suppressor T-cells (T8). Eighty-eight percent of patients had reduced DTH activities. Fifty-six percent of PVFS patients had reduced levels of either IgG1 or IgG3. The authors again propose that PVFS is a consequence of persistent intracellular infection accompanied by a disordered cell-mediated immune response that gives rise to a chronic cytokine-mediated symptomology often called chronic fatigue syndrome.

66: Matteucci, D, M Paglianti, AM Giangregorio, MP Capobianchi, F Dianzani, and M Bendinelli
1985
Group B Coxsackieviruses readily establish persistent infections in human lymphoid cell lines

J. Virol. **56:** 651-654

67: Matteucci, D, A Toniolo, PG Conaldi, F Basolo, Z Gori, and M Bendinelli
1985
Systemic lymphoid atrophy in Coxsackievirus B3-infected mice: effects of virus and immunopotentiating agents
J. Infec. Dis. **151:** 1100-1108
Comment: Generally, the authors establish that certain picornaviruses may cause severe stress-independent lymphoid damage in the absence of viral replication in situ. Three new insights are provided concerning the pathophysiology of Coxsackievirus infections that may extend to other enteroviruses as well: (1) Until *circa* 1985, the pathophysiology of Coxsackievirus infections (particularly the B subgroup) was considered to be a direct consequence of the highly lytic infection of cells by these agents. Subsequent studies, such as those reported, revealed marked immunosuppressive effects of such viruses that could not be attributed to their replication in immunocompetent cells. (2) Coxsackievirus B3 caused severe anatomic and functional changes in lymphoid tissues and organs without replicating in them. (3) Immunopotentiating agents can exacerbate such pathologic changes. The authors suggest that their results did not implicate adrenal mediated stress in the observed lymphoid atrophy. The authors did not suggest that possible contamination of virus stocks by lactic dehydrogenase virus might have contributed to some of the changes seen in atrophied lymphoid tissues (cf. Snodgrass, MJ et al., 1972. *J. Immunol.* **108:** 877).

Contemporary publications

Pub.#:

68: Huber, SA, LP Job, and JF Woodruff
1981
Sex-related differences in the pattern of Coxsackievirus B-3-induced immune cell cytotoxicity against virus-infected myofibers
Infect. Immunol. **32:** 68-73
Comment: The authors note that Coxsackievirus B3-elicited myocarditis in adult mice is restricted to males. This raises the question of whether the higher frequency of PVFS in females may be more sex-related than occupational risk.

69: Irwin, M, TL Smith, and JC Gillin
1987
Low natural killer cytotoxicity in major depression

Life Sciences **41:** 2127-2133
Comment: This is one of many papers in the area of psychoneuroimmunology that show how psychological disorder can affect immunologic functions. A substantial literature has accumulated in this field. Good assessment appoaches exist and should be used (under psychiatric supervision) concerning mental symptomology in patients with PVFS or Gulf War Syndrome; anecdotal information about mental syndromes in relation to immunodeficiency are obviously not sufficient. See: AL Buckman and AI Fins. 1993. **Psychological and cognitive aspects of the chronic fatigue syndrome.** *In* PJ Goodnick and NG Klimas, eds. **Chronic fatigue and related immune deficiency syndromes.** *Progress in psychiatry.*(Washington, D.C.: American Psychiatric Press) **40:** 67-94.

70: Klimas, NG, FR Salvato, R Morgan, and MA Fletcher
1990
Immunologic abnormalities in chronic fatigue syndrome
J. Clin. Microbiol. **28:** 1403-1410
Comment: In an effort to characterize in a comprehensive manner the status of laboratory markers associated with cellular immune function in patients with CFS, the authors established a pattern of immune marker abnormalities that is compatible with a chronic viral reactivation syndrome. This study is distinctive by virtue of the detailed analysis of T-cell subsets; in particular, CD4+ and CD45RA T-cells were depleted in the 30 patients studied. The authors attribute the specific depression to the occurrence of "somewhat higher percentages of CD29+ memory cells as a consequence of chronic virally-induced antigenic stimulation." However, six alternative explanations also were offered. The authors suggest that PVFS is a form of acquired immunodeficiency. Fifty-four references are listed in the bibliography.

71: Linde, A, L Hammarström, and CIE Smith
1988
IgG subclass deficiency and chronic fatigue syndrome
Lancet **i:** 885-886
Comment: Six patients were tested that had symptoms "suggestive of the chronic fatigue syndrome." The duration was more than one year. Two of these had decreased amounts of IgG3. No laboratory data were reported. The authors note that IgG3 deficiency has been correlated with chronic symptoms.

72: Lloyd, A, I Hickie, D Wakefield, C Baughtom, and J Dwyer
1990
A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue

syndrome
Am. J. Med. **89:** 561-568
Comment: This study, like Peterson et al. (**75**), consisted of well-selected patients, most of whom had chronic disease of *ca* four years duration. The authors report that 10/23 (43%) of the PVFS group and 3/26 (12%) of the placebo group benefitted from immunoglobulin therapy. The methodologies used by Lloyd et al. to evaluate patients appear to have been considerably more rigorous than those employed by Peterson et al. Adverse effects observed by Lloyd et al., as stipulated in the text, were not categorized as "major". Some of the patients in both the treatment and placebo groups had a relapse of symptoms several months after therapy was completed. This finding has many interesting interpretations. The asserted resolution by immunoglobulin therapy of abnormalities in cell-mediated immunity and delayed-hypersensitivity skin-test reactivities are of particular interest.

73: Morrison, LJA, WHM Behan, and PO Behan
1991
Changes in natural killer cell phenotype in patients with post viral fatigue syndrome
Clin. Exp. Immunol. **83:** 441-446
Comment: The patients studied by the authors were distinct in that they "all had severe fatigue that had been present for more than 1 year" and included approximately equal numbers of each sex.

74: Murdoch, JC
1988
Cell mediated immunity in patients with myalgic encephalomyelitis syndrome
N. Z. Med. J. **101:** 511-512
Comment: The "Multitest" assay technique was used to compare delayed hypersensitivity reactions (DTH) of 33 well-defined PVFS patients and matched controls. Test antigens were tetanus and diphtheria toxins, and extracts from streptococci, tubercle bacilli, candida spp., Trichophyton spp., and "proteus" spp. Overall, the DTH response of PVFS patients was suppressed, compared to controls. Some, however, were normal, relative to diphtheria toxin, tubercle, candida, and proteus. Possibly the tetanus response also was not different. Given the fact that 15% of the controls registered as anaergic and that Multitest data are inconsistent among diverse population groups, the reported results are difficult to assess.

75: Peterson, PK, J Shepard, M Macres, C Schenck, J Crosson, D Rechtman, and N Lurie
1990
A controlled trial of intravenous immunoglobulin G in chronic

fatigue syndrome
Am. J. Med. **89:** 554-560
Comments: Several points are notable: The 28 selected patients were carefully studied, mostly female, and had CFS for *ca* four years. Low levels of IgG1 (42.9%) and IgG3 (64.3 %) were found in patients before therapy. No therapeutic benefit from treatment was found. Major adverse experiences were observed in 20% of both test and control groups. The reported results appear to differ from those found in similar studies, as reported by Lloyd et al. (see **72**).

76: Prieto, J, ML Subira, A Castilla, and M Sorrano
1989
Naloxone-reversible monocyte dysfunction in patients with chronic fatigue syndrome
Scand. J. Immunol. **30:** 13-20
Comment: This publication, and similar papers by Prieto et al., report that opiates and opioids known to be released during stress can suppress monocyte functions. Monocyte dysfunctions, defined by the authors, that occurred in patients with PVFS, were reversed by treating monocytes in vitro with Naloxone, an opioid antagonist.

77: Read, R, G Spickett, J Harvey, AJ Edwards, and HE Larson
1988
IgG1 subclass deficiency in patients with chronic fatigue syndrome
Lancet **i:** 241-242
Comment: Two patients were studied that had PVFS 16-to-18 months, had a low ratio of T4/T8 cells where studies were initiated, and had no evidence for active or chronic EBV infection. The ages of the female and male patients were 32 and 24, respectively. The initial assays revealed a low concentration of IgG with a deficit in IgG1. Four months after initial studies, the T4/T8 cell ratios returned to normal levels in both patients, but one patient had a persistent IgG1 deficit. The authors point out that IgG1 deficiencies are rare in the general population and, when found, occur in subjects with common variable hypogammaglobulinemia. They suggest that the IgG1 deficit observed may reflect a failure in T-cell help or excess subclass-specific suppression, i.e., the transitory nature of the defect in one patient argues against deletion of IgG1-secreting B-cells.

78: Subira, ML, A Castilla, M-D Civeira, and J Prieto
1989
Deficient display of CD3 on lymphocytes of patients with chronic fatigue syndrome
J. Infect. Dis. **160:** 165
Comment: Twenty well-defined patients and matched controls

were studied. The duration of disease in the patient group ranged from eight months to 14 years, i.e., patients had chronic disease. The results indicated that PVFS patients may have T lymphocytes (CD2 and CD5 positive) without immunoreactive CD3.

Cytokines in the Pathogenesis of PVFS

Systematic long-term studies of cytokine levels in patients with PVFS are largely lacking. An important need is to determine serum and cerebrospinal fluid cytokine levels over the course of disease (see **83**), since there may be a cascade effect at given times. The occurrence of signs and symptoms roughly analogous to those found in patients with PVFS that occur in patients treated with cytokines (**81, 84, 87**) imply an etiologic role of cytokines in the pathogenesis of PVFS. As noted below, clearly aberrant levels of cytokines have not been found consistently in patients with PVFS.

Pub.#:

79: Chao, CC, EN Janoff, SX Hu, K Thomas, M Gallagher, M Tsang, and PK Peterson
1991
Altered cytokine release in peripheral blood mononuclear cell cultures from patients with the chronic fatigue syndrome
Cytokine **3:** 292-298
Comment: The authors measured the levels of cytokines in the serum of patients with PVFS and also measured the release of cytokines from cultured peripheral blood monocyte (PBMC) after stimulation with either lipopolysaccharide (LPS) or phytohemagglutinin. Only serum levels of transforming growth factor-beta (TGF-beta) were elevated. PBMC stimulated with LPS, when compared with controls, released increased amounts of IL-1, IL-6 and TNF-alpha. Paradoxically, the amount of TGF-beta was decreased.

80: Cheney, PR, SE Dorman, and DS Bell
1989
Interleukin-2 and the chronic fatigue syndrome
Ann. Internal Med. **110:** 321
Comment: Plasma levels of interleukin-2 (IL-2) were determined in 104 patients with accurately diagnosed PVFS and 22 sex- and age-matched controls. The mean plasma levels in the PVFS patients were *ca* 55.8 U/ml and 1.4 U/ml for controls. The observed difference was statistically significant, but failed to correlate with severity or duration of disease. "A greater frequency of very high values (7/50 U/ml) was seen in patients younger than 20 years of

age who were purposefully omitted from this adult study."

81: Denicoff, KD, DR Rubinow, MZ Papa, C Simpson, CA Seipp, MT Lotze, AE Chang, D Rosenstein, and SA Rosenberg
1987
The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells
Ann. Internal Med. **107:** 293-300
Comment: Table 8 in this paper lists the clinically significant neuropsychiatric abnormalities that occurred in patients treated with IL-2. Forty-four patients with metastatic cancer were studied. The signs and symptoms listed in Table 8 are similar to those described by McDonald and Mann (**84**) and also show a commonality with those found in patients with PVFS.

82: Lever, AML, DM Lewis, BA Bannister, M Fry, and N Berry
1988
Interferon production in the postviral fatigue syndrome
Lancet **ii:** 101
Comment: Eight children with PVFS of three-to-five months duration were studied along with four age-matched controls. Peripheral blood mononuclear cells were assayed for alpha interferon production. The authors report that children with PVFS produced significantly more interferon than controls.

83: Lloyd, AR, D Wakefield and I Hickie
1993
Immunity and pathophysiology of chronic fatigue syndrome
In R Jenkins and JF Mowbray, eds. *Chronic fatigue syndrome. Ciba Foundation Symposium* **173:** 176-187. New York: J Wiley & Sons
Comment: In the section of the review allocated to effects of cytokines on the pathogenesis of PVFS, the authors noted that there were only elevations in the serum levels of transforming factor beta and IL-1. Lloyd et al. comment that their studies disclosed only a marginal increase in interferon-alpha. The authors make a valuable assessment of the varous problems associated with evaluating cytokine levels in PVFS patients. For example, only single samples are usually tested, despite the recognized fact that cascades of cytokines occur during the course of an immune response, and it is probable that they are neither quantitatively or qualitatively equivalent at different points of time.

84: McDonald, EM, AH Mann, and HC Thomas
1987
Interferons as mediators of psychiatric morbidity
Lancet **ii:** 1175-1177
Comment: This study is quoted widely in the literature as

documentation for psychiatric syndromes elicited by IFN-alpha used therapeutically. In fact, the publication reports an array of additional interesting and important findings. But the paper focuses on an association between treatment of patients with IFN-alpha and psychiatric morbidity. The patients studied were males, 18-58 years of age, most were homosexual, some had HIV-1 infection, and many had antecedent psychiatric problems (34% of the therapy group and 46% of the controls). IFN-alpha was used to treat the hepatitis-B carrier state. In the therapy group, 17/27 "became psychiatric cases". This was most frequent in the HIV-1 subgroup. The "psychiatric symptoms seem[ed] to be non-psychotic, the most commonly reported being fatigue, impaired concentration, anxiety and depression." The authors comment that the most commonly reported adverse reactions to INF-alpha are fatigue, drowsiness, disorientation, slowness and withdrawal---all suggestive of impaired cerebral function, organic in nature, and confirmable by electroencephalography. Clearly, some of the signs and symptoms characteristic of PVFS may be attributable to cytokines.

85: McDonald, E and A Mann
1991
Interferon in viral illness and myalgic encephalomyelitis
In R Jenkins and J Mowbray, eds. *Post-viral fatigue syndrome (myalgic encephalomyelitis).* New York: J Wiley & Sons
Comment: In a clear and straightforward way, the authors briefly review the role(s) of interferon (IFN) in viral diseases and discuss the possible role(s) of IFNs in the pathogenesis of PVFS. The results of IFN studies on 112 patients with PVFS are summarized. Increased levels of IFN in the sera of such patients were not found. In a limited study involving eight children (see **82**), it was reported that their peripheral blood monocytes produced more IFN than those of controls. The authors did not report on studies of IFN in the cerebrospinal fluid of patients with PVFS. The review includes 40 citations.

86: Patarca, R, MA Fletcher, and NG Klimas
1993
Immunologic correlates of chronic fatigue syndrome
In PJ Goodnick and NG Klimas, eds. *Chronic fatigue and related immune deficiency syndromes. Progress in Psychiatry* **40:**1-21. Washington, D.C.: American Psychiatric Press
Comment: In their summary, the authors comment that patients with PVFS have "two basic problems with immune function: (1) chronic immune activation [in which there are elevations of circulating cytokines] and (2) poor cellular function with low NK cell cytotoxicity, poor lymphocyte response to mitogens, and frequent immunoglobulin deficiencies, most often with IgG1 and IgG3." In

the authors' report of their studies, they state that the serum levels of cytokines in the patients studied were: 18% had elevated levels of IL-2; IL-4 levels were normal; 12% had elevated levels of soluble receptor for IL-2; 12% had elevated levels of neopterin; and 20% had elevated levels of IFN-alpha. The authors could not detect IFN-gamma. Overall, the review is clear and precise. No laboratory data are presented, and the patient and control groups are not documented. The bibliography includes 109 citations.

87: Smedley, H, M Katrak, K Sikora, and T Wheeler
1983
Neurological effects of recombinant human interferon
Brit. Med. J. **286:** 262-264
Comment: The 10 women in the described study group were 42-69 years of age, and 7/10 had mastectomies. The described, limited clinical trial employed "highly purified human leukocyte A interferon (IFN) produced by recombinant DNA technology." The major adverse effects were profound lethergy in 6/10 patients; 5/10 developed frank confusion, loss of concentration and expressive dysphasia. Baseline electroencephalograms allowed detection of abnormal tracings four weeks after treatment. The authors point out that interferon does not cross the blood-brain barrier and cannot be detected in cerebrospinal fluid, even when there are high blood concentrations in patients receiving IFN therapy.

88: Straus, SE, JK Dale, JB Peter, and CA Dinarello
1989
Circulating lymphokine levels in the chronic fatigue syndrome
J. Infec. Dis. **160:** 1085
Comment: In this study, 18 women and seven men with documented PVFS and 25 age- and sex-matched controls were studied. Serum and plasma levels of alpha, beta-1, gamma, IL-2, and TNF were determined. The authors could not demonstrate consistently elevated levels of any of these lymphokines in PVFS patients.

Pathophysiology of PVFS

The pathophysiology of PVFS is complex. There are three main problems: (1) None of the signs or symptoms typical of the syndrome are distinct enough to provide a clear-cut indication of cause. (2) Neither histopathologic, biochemical, nor ultrastructural analyses of biopsy specimens have provided a definition of a central pathologic process. (3) Although the pathophysiology of the disease

is clearly multifactorial, none of the individual interactive elements is sufficiently aberrant to be ascribed a primary role in the pathogenesis of the syndrome. If it is agreed that no single disease marker is pathognomonic, the requirement is to develop and apply patterns of recognition that are diagnostic. Such a strategy requires a departure from conventional diagnostic approaches in clinical laboratory medicine. Computer-based techniques abound that could be applied to such an analysis. Largely, these have not been employed.

This section of the report focuses mainly on two aspects of the pathophysiology of PVFS: (i) myalgia and its possible causes (**89, 91, 93, 95-98, 100**) and (ii) putative control CNS involvement affecting the so-called hypothalamic-pituitary-adrenal axis (**90, 92, 94, 99**). Detailed discussions of the pathophysiology of PVFS are presented in the excellent mongraph: R Jenkins and J Mowbray, eds. *Post-viral fatigue syndrome (myalgic encephalomyelitis),* New York: J Wiley & Sons, 1991. The chapters on pathologic changes in skeletal muscle (TJ Peters and VR Preedy) and on neurophysiological findings (GA Jamal) are very good.

Pub.#:

89: Arnold, DL, GK Radda, PJ Bore, P Styles, and DJ Taylor
1984
Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a post-viral exhaustion / fatigue syndrome. A 31P nuclear magnetic resonance study
Lancet **ii:** 1367-1369
Comment: The metabolic abnormality described by the authors resulted from the study of one patient by NMR. The patient's PVFS occurred as a sequale to varicella virus infection that caused clinically apparent chickenpox at age 26, which is infrequent.

90: Bakheit, AM, PO Behan, TG Dinan, CE Gray, and V O'Keane
1992
Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome
Brit. Med. J. **304:** 1010-1012

91: Behan, PO, WMH Behan, and EJ Bell
1985
The postviral fatigue syndrome - an analysis of the findings in 50 cases
J. Infect. **10:** 211-222
Comment: The authors report that muscle biopsies disclosed abnormal results in 20/20 patients studied. In 15/20, widely

scattered necrotic muscle fibers were identified without an accompanying inflammatory infiltrate. All 20 patients had moderately increased size and numbers of Type II fibers. Mitochondria were increased conspicuously at the periphery of fibers. Conventional electromyography disclosed primary muscle lesions in 30/40 patients. NMR studies revealed abnormal muscle metabolism in 6/6 patients studied. The authors state that, during exercise, there was early intracellular acidosis in muscle suggestive of a disorder of regulation. The described results are interesting to compare with those reviewed by Edwards et al. (**95**). This publication is also **61** above (with a different focus of comments).

92: Bell, DS
1994
Chronic fatigue syndrome update
Postgrad. Med. **96:** 73-81
Comments: This review is clear and refreshing. The central theme is that there may well be a causal relationship between CNS dysfunction and much of the symptomology that characterizes PVFS. Bell summarizes the studies of Bakheit et al. (**90**) on pituitary and hypothalamic abnormalities, and the preliminary work of Demitrack et al. (**94**) on neurotransmitter abnormalities, in support of this central notion. In a sense, it may be considered a refined statement of early hypotheses concerning the pathophysiology of PVFS.

93: Byrne, E and I Trounce
1987
Chronic fatigue and myalgia syndrome: mitochondrial and glycolytic studies in skeletal muscle
J. Neurol. Neurosurg. Psych. **50:** 743-746
Comment: The findings reported by Byrne and Trounce failed to disclose "a major defect in muscle intermediary energy pathways" in the PVFS. Since NMR studies were not done, the results do not necessarily contradict those of Arnold et al. (**89**). Since electron microscopy studies were not done, the results reported do not necessarily contradict those found by Gow and Behan (**37**), who reported "obvious evidence of mitochondrial damage" in 45/60 cases they studied.

94: Demitrack, MA, PW Gold, JK Dale, DD Krahn, MA Kling, and SE Straus
1992
Plasma and cerebrospinal fluid monoamine metabolism in patients with chronic fatigue syndrome: preliminary findings
Biol. Psychiatry **32:** 1065-1077
Comment: Demitrack believes that abnormalities in the

hypothalamus-pituitary-adrenal axis may play a key role in the pathophysiology of PVFS. His excellent paper on the subject should be consulted: **Neuroendocrine research strategies in chronic fatigue syndrome.** *In* PJ Goodnick and NG Klimas, eds. *Chronic fatigue and related immune deficiency syndromes. Progress in Psychiatry* **40:** 45-66. Washington, D. C.: American Psychiatric Press, 1993.

95: Edwards, RHT, H Gibson, JE Claque, and T Helliwell
1993
Muscle histopathology and physiology in chronic fatigue syndrome
In R Jenkins and JF Mowbray, eds. *Chronic fatigue syndrome. Ciba Foundation Symposium* **173:** 102-131. New York: J Wiley & Sons
Comment: The detailed and careful studies summarized by the authors did not indicate that fatigue in PVFS was a result of myopathy. In the described study, "fatigue" was defined to mean the failure to sustain force or power. Fatigue was classified neurophysiologically according to site of origin (central or peripheral). The response to objective electrophysiological assessment was classified as high or low frequency fatigue. For example, the central category correlates with failure of neural drive, i.e., the failure to sustain maximal recruitment of neural motor units or firing frequency. High frequency fatigue signifies impaired neuromuscular transmission or conduction of action potential. Low frequency fatigue was characterized by impaired excitation-contraction coupling. In other words, fatigue is physiologically definable and not some vague abstraction.

96: Friman, G, JE Wright, NG Illback, WR Beisel, JD White, DS Sharp, EL Stephen, WL Daniels, and JA Vogel
1985
Does fever or myalgia indicate reduced physical performance capacity in viral infections?
Acta Med. Scand. **217:** 353-361
Comment: In this very interesting (albeit limited) study, the authors propose that, in brief viral infections, impaired muscle performance correlates with subjective symptoms such as myalgia, while decreased cardiac output correlates with febrile reaction.

97: Jamal, GA and S Hansen
1985
Electrophysiological studies in the post-viral fatigue syndrome
J. Neurol. Neurosurg. Psych. **48:** 691-694
Comment: The authors report important findings: *Ca* 75% of 40 patients with PVFS had single-fiber electromyograph abnormalities,

i.e., evidence of abnormality in the peripheral component of a motor unit. Such a result suggests disturbed muscle-fiber conduction, i.e., the "high frequency fatigue" discussed by Edwards et al. (**95**).

98: McCluskey, DR
1993
Pharmacological approaches to the therapy of chronic fatigue syndrome
In R Jenkins and JF Mowbray, eds. *Chronic fatigue syndrome. Ciba Foundation Symposium* **173:** 280-297. New York: J Wiley & Sons
Comment: The work capacity of patients with PVFS was compared with normal healthy subjects and a group of patients with irritable bowel syndrome, using a modified Bruce stress test. Overall, PVFS patients had reduced aerobic work capacity, higher heart rates, and higher whole-blood lactic acid levels. Subjective observations were interesting: PVFS patients had a grossly abnormal perception of their physical exertion and their premorbid level of physical fitness.

99: Montague, TJ, TJ Marrie, GA Klassen, DJ Bewick, and BM Horàcek
1989
Cardiac function at rest and with exercise in the chronic fatigue syndrome
Chest **95:** 779-784
Comment: The authors conclude from their studies that patients with PVFS "have normal resting cardiac function but a markedly abbreviated exercise capacity characterized by slow acceleration of heart rate and fatigue exercising muscles long before peak heart rate is achieved." These are important findings. However, examination of patient documentation (Table 1) disclosed that, of the 40 patient test group, 13 had fatigue of less than five months duration, thus contracting the valid test group to 27. Of these, 24 were between 20-57 years of age (mean=28). In this group, 15 were females and nine were males. In the other age category, patients were 58, 59, and 70 years of age, respectively. The 70 year old patient was female. It was not clear how such distributions affected results. Nonetheless, the authors make the interesting suggestion that their data are compatible with latent viral effects on cardiac pacemaker cells or their autonomic control, an observation of clinical relevance.

100: Schiller, HH, MS Schwartz, and G Friman
1977
Disturbed neuromuscular transmission in viral infection
N. Engl. J. Med. **296:** 884
Comment: The important findings summarized here are rarely

cited in the literature. Single-fiber electromyography (SFEMG) was used to investigate causes of myalgia in type A influenza virus infection. Virus particles are known to be detectable in motor endplate regions. In a study of 14 patients, disturbances in neuromuscular transmission were found that appeared to be related to the viral associated myalgia.

101: Wakefield, D and A Lloyd
1987
Pathophysiology of myalgic encephalitis
Lancet **ii:** 918-919