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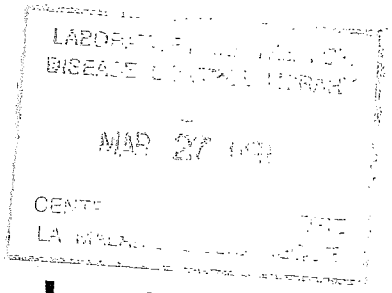

Proceedings of a Workshop
CHRONIC FATIGUE SYNDROME

Toronto, Ontario
28-29 September 1989

Health and Welfare Canada
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Organized by
the Laboratory Centre for Disease Control
Health Protection Branch
Department of National Health and Welfare

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Session A
Clinical and Psychiatric Features

1. Welcome and Introduction

J.H. Joncas

On behalf of the Laboratory Centre for Disease Control I want to welcome you to this workshop on chronic fatigue syndrome (CFS). The purpose of this meeting is to review what we know about CFS, make recommendations and prepare guidelines concerning the diagnosis and management of CFS, and discuss various approaches for future research.

CFS was first thought to be associated with an active and persistent Epstein-Barr virus (EBV) infection and was often called chronic mononucleosis. Other viruses were subsequently suspected, human herpesvirus 6 (HHV6) among others, and the syndrome has come to be viewed as a post-viral-infection syndrome.

By way of introduction I would like to suggest that, on the contrary, CFS may primarily be a metabolic disorder which could secondarily induce the reactivation of several persistent but usually latent viral infections. Alternatively, but less likely I think, the metabolic disturbances could primarily or more directly be triggered by virus infection or reactivation, a bit like intestinal disaccharidase deficiency when an intolerance to milk follows a viral or bacterial gastroenteritis. These 2 hypotheses, however, are not mutually exclusive since a primary metabolic disorder may induce reactivation of a viral infection, which in turn could trigger additional metabolic disturbances. The reason why I favor this hypothesis is mainly because well-documented chronic active viral infections (such as from EBV, for instance) were not, in our experience, usually associated with chronic fatigue. Furthermore, excessive or persistent fatigue is usually not a prominent feature of other persistent or chronic viral infections, except in the convalescent phase of a few viral diseases such as hepatitis, infectious mononucleosis, and influenza in a few patients (Table 1). These post-viral-infection fatigue syndromes, however, rarely last more than a few weeks or a few months.

Most of the clinical features of CFS and of its associated disorders could be elicited by the various biologic amines and corticosteroids which could be produced in excess as a result of the chronic stress experienced for many years by a large majority of patients seen with this syndrome (Figure 1). These metabolites, catechol amines and glucocorticoids, are able to reactivate latent herpesvirus infections *in vitro* as well as *in vivo*[1,3,4,5]. Acute and reactivated herpesvirus infections, on the

Table 1.
Chronic Viral Infections With or Without Disease in Man

Virus	Infected Cells	Disease	Fatigue Following Acute Infection
Hepatitis B	Hepatocyte PMBC, T, B lymph	Chronic active hepatitis, hepatocarcinoma, ICD, vasculitis	Short period ±
Non A non B Hepatitis	Hepatocyte	Chronic active hepatitis	Short period ±
Polyoma JC	PBMC, BM, neuronal and glial cells	PML	
BK	renal tubular epithelium	Proliferation and obstruction	
Papilloma	Epithelial cells	Warts	
Adenoviruses (group C)	T, B, null lymph, tonsil	Bronchiolitis obliterans?	
HSV	T lymph, neuroganglial	Vesicles, encephalitis	
VZ	neuroganglial	Zoster, encephalitis	
CMV	Lymph, mono, renal, etc.	Pneumonia, chorioretinitis, hepatitis...	
EBV	B lymph, oral epithelium	B cell lymphona, pancytopenia...	Variable period ±
Pox	Epithelial cells	Molluscum contagiosum	
HTLV1	T, B, null lymph	T cell leukemina, tropical spastic paraparesis	
HTLVIII (HIV)	T, B, lymph, mono	AIDS	
Rubella	T and B lymph	CRS, panencephalitis	
Measles	T and B lymph, mono	SSPE	
Influenza A?	lymph, mono	Parkinson's?	Short period ±
Rabies ?	CNS	Delayed encephalitis (1 year)	
Enterovirus ?	Muscle, pancreas	Dermatomyositis-like disease, juvenile diabetes?	
Prions	CNS	Kuru, Creutzfeldt-Jacob	

Figure 1
CFS Signs and Symptoms

Severe fatigue
Post-exertional fatigue and malaise – decreased muscular strength
Headache
Myalgias
Difficulty concentrating
Dizziness
Depression – anxiety
Paresthesias
Arthralgia
Night sweats
Chronic cough
Pharyngitis
Low-grade fever
Lymphadenopathy
Recurrent sore throat

Chronic stress with increased catechol amines and glucocorticoids production

Cytokines and lymphokines produced in response to reactivated infections

Associate disorders
Recurrent hives
Anxiety attacks
Functional bowel syndrome
Premenstrual syndrome
Candida albicans infections

Figure 2
CFS Immunologic Abnormalities

↑ NK
↑ Interferon
↑ IL2
↑ B lymphocytes
↓ Gammaglobulins
Partial hypergamma
↑ T4/T8 ratio
NMR abnormalities
↓ Low IGA ab
Circulating immune complexes
↑ HHV6 ab
↑ EBV-VCA-EA ab
Other markers of persistent viral infections (adeno...)

Reactivated viral infections of lymphoid and neural cells

other hand, have been associated with many, if not all, of the immunologic abnormalities (Figure 2) seen in some patients with CFS[2,6,7,8,9]. Upon recovery from these infections, these abnormalities disappear. In turn, many of the CFS symptoms and signs (Figure 1) can result from cytokines and lymphokines produced in reaction to such viral infections or their reactivation. This may be the case for headache, low-grade fever, myalgias, and fatigue, to name only a few. Viral reactivation, through induced cytokines and lymphokines, could therefore contribute to many of the features of CFS. Finally, it is also not excluded that virus reactivation could cause some of the neurologic and immunologic features and abnormalities seen in CFS in a more direct way: cells of the lymphoid and nervous systems are among the least permissive cells to virus replication but are the prime targets of latent infections (Table 1)[10]. It would not be too surprising if reactivation of a virus within these cells could directly disturb their specialized functions, giving rise to some of the clinical and laboratory features of CFS.

In summary, CFS may be the active expression of an underlying primary metabolic disorder revealed by chronic stress and resulting in the reactivation of latent viruses, with such reactivation, in turn, contributing to the full expression of the syndrome. Therefore, underlying enzyme deficiencies involved in the metabolism of biologic amines and corticosteroids should be looked for in future research on the syndrome. The often-made observation that patients with CFS have reduced tolerance to alcohol and drugs, and that they have an increased incidence of allergic manifestations, also suggests the possibility of an underlying deficiency of one or more enzymes involved in the degradation of these compounds or of mediators of allergic reactions, such as histamine. Alternatively, an impaired endogenous corticosteroid response to allergens and intoxicants may account for these observations. Investigations along these lines may also, therefore, be rewarding.

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2. *Myalgic Encephalomyelitis (Chronic Fatigue Syndrome): An Historic Perspective*

B.M. Hyde

Introduction

There have been several viral theories of the cause for myalgic encephalomyelitis (ME) postulated over the past 45 years. The principal theories are as follows:

1. **Simple Uni-Enterovirus Theory:** one of the following viruses can cause ME: poliovirus[1], coxsackie virus[2], and echo group of viruses[3].
2. **Multiple Enterovirus Theory:** any or all of the above viruses are capable of causing ME[4].
3. **Precursor + Multiple Enterovirus Theory**[5] an initial immune injury occurs which may be of a temporary or chronic nature and is followed by the causal infection with any of the enteroviruses. This initial immune injury can be due to infection of a different or the same group of viruses or can be due to non-viral immune system injury.
4. **Simple Uni-Herpesvirus Theory:** one of the following herpesviruses causes ME[6,7,8]:
   Epstein-Barr virus (EBV)
   Cytomegalic virus
   human herpesvirus 6 or roseola virus 1 (HHV6)
   Inoue-Melnick virus
   varicella-zoster (chickenpox) virus.
5. **Multiple Herpesvirus Theory:** any or all of the herpesviruses (above) are capable of causing ME.
6. **Retrovirus Theory**[9,10]: a retrovirus, similar in action but different from the acquired immunodeficiency syndrome (AIDS) virus, can cause ME.
7. **Common Precursor Retrovirus Theory** (see presentation 9): a common precursor to AIDS and ME exists. This may be HHV6 or some other yet unknown virus or viral-like body.

It is the third theory that the Nightingale Research Foundation uses as its working premise. Subjective evidence suggests that there is a lack of significant viral studies funded for ME and that this is part of the reason why current information in this area is ambiguous.

This article will discuss the history of ME-like disease and the enterovirus or polio-like viruses and their probable role in the cause of ME. Let us first look at the history.

History

The origins of ME are ancient. A disease complex that may have been ME was described in 1900 B.C. and is partially preserved in a papyrus fragment from that date. It is obvious that the origins of this text were considerably older. A complete copy of that information exists in the papyrus Ebers and is dated circa 1400 B.C.[11]. Much of the mythology of ME was incorporated into western medicine at the time of Hippocrates in the fourth century B.C. and later taken up by Galen in the second century A.D. Galen, in fact, was one of the first to suggest that the disease complex known today as ME was related to physical disease and not hysteria. His view was not heeded.

For most of the next 2,000 years there were very few physicians who believed that ME or any disease had an infectious cause. The theory of infection, though hinted at by the atomists, was never seriously entertained. The early Egyptian mythology that any unexplained illness is simply due to the gods or hysteria has never died but has simply been clothed in the modern pseudoscientific terminology of the day and has persisted with few critics for most of the last 2,000 years.

The first epidemic of what appears to have been ME to strike an English-speaking country arrived in England from Holland at the time of Henry VIII[12]. In fact one of his several wives, Anne Boleyn, fell ill during this epidemic, then called "The English Sweats"[13]. But medical language was rarely written in such a manner that we can be absolutely sure of what they were talking about. This lack of adequate description changed in the 1650s when ME was first described by "the English Hippocrates," Thomas Sydenham. Even then, ME had several names. It was described by physicians in various ways including "muscular rheumatism," while the common public name at the time was simply "The English Disease"[13]. One of Sydenham's remedies for the many muscle aches of ME was Balm of Gilead. It probably was the first symptomatic ME medication that actually worked. Let me describe how to compound this first English prescription for ME:

> Mix one pound of the best bees wax over a moderate fire in a like quantity of canary wine. Add of the best olive oil and Venice turpentine washed to whiteness in rose water, add half a pound. Evaporate the wine by boiling at a gentle heat. Remove the mixture from the fire, and add two ounces of red sandal wood, finely powdered. Stir until cool[13].

From this preparation one learns why the British were obliged to become a seafaring nation. This exotic balm was applied externally. Not only did this balm assist the muscle aches, it undoubtedly improved many a patient's perfume.

In 1854, the very active Florence Nightingale, while organizing the field services for the British Army, succumbed to an infectious disease in the Crimea. She recovered briefly only to fall ill again. At 35 she had been an extraordinary worker and had worked for years with a diligence that would have exhausted the most hardened general. She became chronically ill with chest pain, headaches, and a rapid muscle fatigue that lasted until she was 60 years of age. She had persistent upper back pain. Numerous heart specialists failed to find any cardiac disease or, for that matter, any other disease. She would take a short, halting walk in the garden in front of her house but was unable to walk any distance and frequently had to be carried. She was unable to concentrate when more than one person spoke to her and so received only private audiences of one or two persons. Yet, isolated physically from the world in her bed and chambers, she reorganized the British hospital and health services, developed

and pushed through the architectural concepts for British hospital construction, started a school of nursing, and organized the field services for the Prussian army and the sewer system of Calcutta. We name our Foundation after Nightingale since it is highly likely that she suffered either from ME or a disease indistinguishable from it[14].

In 1856, Finsen[15] observed an epidemic of muscle rheumatism and chest pain in Iceland. This was probably the first recorded coxsackie epidemic, later to be called Bornholm disease, and one of the several precursors of ME. The same epidemic repeated itself in a more serious fashion in Iceland in the district of Ofjord in 1865[15].

In the American Civil War, ME surfaced as "Soldiers' Disease" and the neurologist-in-chief for the Union Forces, Silas Weir Mitchell, published a book on this disease. The book was largely concerned with treatment, proposing total bed rest and hypernutrition for a period of several months[16].

The Paralytic Years, 1881-1955

Despite the work of Jenner of smallpox fame and other important scientific workers, until approximately 1880 very few physicians thought in terms of or even believed in infectious diseases or the concept of microbes as causing disease. In 1881 this all changed with the first recorded epidemic of paralytic poliomyelitis. This epidemic[17] of 18 cases occurred in northern Sweden. Almost simultaneously another small epidemic of 5 cases appeared in Norway. In 1885 an epidemic of 13 cases occurred in southern France. By 1890[18], when an epidemic of 44 cases of poliomyelitis struck Stockholm, paralytic poliomyelitis was at epidemic proportions as far away as California. In Sweden in 1905, Wickman[19] described the first of the colossal epidemics that were to occur. In this first macro-epidemic, 1,031 cases were recorded in Stockholm, while a simultaneous and similar epidemic took place in Norway.

Blind to the increasing information indicating that poliomyelitis was due to an infectious process, as late as 1901 Déjerine[20] in France insisted that paralytic poliomyelitis was the result of a psychologic predisposition. It is a view proposed by some physicians today when discussing ME.

By 1913[17] Wickman was already beginning to document the first of several camp followers of paralytic poliomyelitis. Said to be suffering from abortive poliomyelitis, these patients experiencing weakened muscles and sensory injury never progressed to the paralysis typical of poliomyelitis. He also noted cases of recurrent poliomyelitis. Before long, these were joined by posterior or sensory poliomyelitis in which the patient had muscle pain and weakness but not paralysis.

It was not until the full-blown poliomyelitis epidemic that swept California in the summer of 1934[1] that ME was actually recognized as a separate epidemic disease. During that poliomyelitis epidemic another and different type of epidemic occurred among the personnel of the Los Angeles County General Hospital. There were no deaths and 198 or more cases occurred among the nurses, physicians, ambulance drivers, and other medical support staff.

It is important to note that the 1934 epidemic followed as part of a larger California epidemic in which 1,301 cases of paralytic poliomyelitis were hospitalized in the Los Angeles General Hospital alone. Another 1,198 that presented were diagnosed as **not having poliomyelitis.** What did they have? It is quite probable that many had ME, but when there were 1,301 paralyzed and dying cases of poliomyelitis, ME patients would have been rightly dismissed as unimportant. It is perhaps for this reason that recorded epidemics of ME were largely reported among doctors and nurses, individuals who, due to their proximity, could not be ignored.

The investigation of this 1934 epidemic by the Past Assistant Surgeon of the United States Public Health Services, Dr. A.G. Gilliam, was not published until 4 years after the event, in 1938. Dr. Leake, Medical Director, United States Public Health Services, makes a point in the foreword of *Public Health Bulletin, No. 240* of stating that "none of these cases is definite poliomyelitis." The report was, nevertheless, published by Gilliam as *An epidemic, diagnosed as poliomyelitis.*

Though a lot is known about the epidemic itself, little is known about what happened to the 198 doctors and nurses concerned and, although 54 years later I have been able to track down some of the surviving doctors, I have yet to contact any of the nurses, a few of whom must still be alive. Part of the reason for the lack of published follow-up is the fact that the 198 staff members sued the hospital and eventually settled for $6 million in 1939. Such an amount in 1939, divided among the group, would have purchased 3 houses in the best section of Los Angeles. Contingent on receiving the payment was non-publicity of the epidemic.

It is apparent from the work of Gilliam[1] that the large majority of the medical staff fell ill with ME after being injected with immune prophylactic globulin prepared from the serum of those who had fallen ill during this epidemic. Was this the first recorded clinical transfer of ME? The majority of these health-care workers have never fully recovered.

The symptoms of this epidemic were those of ME. The patients developed relapsing muscle weakness, unusual pain syndromes, personality changes, memory loss, aphasias – all typical ME symptoms. Many of the staff doctors never returned to full employment although they were all very young at the time. The nurses in particular were all treated as having hysteria and as late as 1968 Marinacci writes, tongue in cheek, that **all** of the nurses affected in the 1934 epidemic had been hysterectomized as a technique to treat their hysteria, and that the surgery had not helped[21]. This first, carefully recorded, epidemic disease came to be called atypical poliomyelitis.

Up until 1955, when general poliomyelitis immunization was introduced, many, if not most, of the ME epidemics occurred concurrently with or followed epidemics of paralytic poliomyelitis. After the introduction of poliomyelitis immunization, paralytic poliomyelitis stopped but ME persisted.

But the nature of ME itself also changed. When you investigate any large numbers of these pre-1955 ME patients, as I have done, it is not hard to observe that many are paralyzed and in wheelchairs. When post-1955 ME patients are examined, severe muscle failure is common, but paralysis is for all purposes totally lacking. This paralytic

facet of ME is last described in the ME literature by Acheson[22]. This large review of epidemic ME is well-worth reading. It describes an epidemic disease process that is identical to endemic ME now with one exception: today, in the western world, there are no associated cases of paralysis. Clearly the introduction of poliomyelitis immunization has had an effect on preventing paralysis in ME patients. Since 1955 there have been no more records of death or paralysis in ME epidemics. Clearly this suggests a viral connection between ME and poliomyelitis.

The 1936 Wisconsin epidemic of ME occurred when a student nun returned to her cloistered school from Brooklyn[22]. Her friend in Brooklyn developed poliomyelitis at the same time as the student nun fell ill with ME. It appears that the novice from Brooklyn was the source of the epidemic that followed in her dormitory. Up to 1942, 3 epidemics of ME in Switzerland were called abortive poliomyelitis[23]. The 1948 epidemic in Iceland started as a poliomyelitis epidemic[24,25] and finished as a major ME epidemic involving 1,116 patients. The non-stop 1949-51 ME epidemic in Adelaide, South Australia[26, 27, 28, 29], was associated with an epidemic of paralytic poliomyelitis. The 1951 ME epidemic in upper New York State, described by Dr. White of Queen's University, Kingston[30], was associated with a poliomyelitis epidemic. In 1953, the ME epidemics in both Copenhagen, Denmark[31, 32], and Coventry, England[33], were associated with poliomyelitis, as was the Royal Free epidemic[34]. Another name for ME was Coventry Disease and it was this name that was used by the ME patients in Pittsfield, Massachusetts[35].

The 1956 Pittsfield outbreak combined ME and poliomyelitis. This reputedly started when an American airman was brought home from Iceland with paralytic poliomyelitis. His arrival in Pittsfield started a mixed polio-ME epidemic.

This poliomyelitis-ME association is so constant that it becomes boring to even recount the events. Patients with ME symptoms were generally abandoned and forgotten in the midst of the epidemic turmoil. There was no time for them. The medical and nursing staff were usually exhausted from caring for the enormous numbers of dying and paralyzed patients.

The Poliovirus Theory of ME is Also Abandoned

After 1955 and the general introduction of polio immunization, people stopped falling ill with both paralytic poliomyelitis and paralytic ME but non-paralytic ME continued. Since poliomyelitis no longer existed as a major public health problem in the temperate climatic zones, it was only normal to conclude that the continuation of ME must have been due to another virus or group of viruses. This conception, of course, was based upon theories of poliovirus immunization.

These theories frame our entire understanding of poliomyelitis and were responsible for ME researchers abandoning the polio theory as a cause. For 35 years researchers have looked for another cause. To date, they have met with considerable failure. Before proceeding to discuss other agents, let us make a few final comments on poliomyelitis.

Poliomyelitis is caused by death or injury to the anterior horn cells. These anterior horn cells exist in the anterior part of the spinal cord. Other cells in the lower part of the brain were also attacked in some cases of poliomyelitis. These "motor" cells were responsible for the normal muscle stimulation and function. With the death of these anterior horn cells, innervation to the muscles was interrupted and the muscle "died." But why were these anterior horn cells or other motor cells selectively destroyed or injured in poliomyelitis?

Anterior horn cells have specific receptors for paralytic poliomyelitis viruses. The virus is capable of paralyzing only because it has a specific reciprocal receptor on the motor nerve cell.

Simply stated, polio immunization may work not just by an increase in the antibody response to polioviruses that are capable of causing paralytic poliomyelitis but by a selective blockade by non-virulent poliovirus vaccine strains of the receptors in the anterior horn and other motor cells.

In August of 1989 we received a call at the Nightingale Research Foundation from the Provincial Viral Laboratories. One of our patients had a dangerous rising titre to polio 3 virus. "Is she in the hospital? Is she paralyzed?" "No," I said, "she has simply got ME." She happened to be one of the few ME patients for whom we could tell exactly what virus had caused her illness.

At the Nightingale Research Foundation we believe, like Albert Sabin, that many of the enteroviruses cause paralytic "poliomyelitis." We also believe that many of the enteroviruses cause ME. It is a fact that the majority of ME patients today, as well as in the post-1955 period, are not in high-stress occupations as the popular press frequently suggests, but are teachers, nurses, physicians, and other health-care workers. This group represents those most closely related to infectious illness, frequent immunizations, and those most frequently immunized. Up to 1955, recognized ME was clearly previously associated with poliomyelitis. Many of the symptom complexes associated with poliomyelitis epidemics we call ME today. In the past we attributed these findings to abortive polio, atypical polio, or posterior polio. The viruses that cause paralytic poliomyelitis are some of the same viruses that cause ME. But these enteroviruses that are capable of causing paralysis attach to more than one set of tissue receptors. These other receptors are found on different cells in the brain and spine as well as in other body areas. The symptoms described by ME sufferers are due to injury to these other cells.

In North America, subjective observations would indicate that very little of the global viral research budget is dedicated to investigation of enteroviruses. Without heed, we are sitting on the edge of a cliff, waiting for disaster. For many sufferers of ME that disaster is already here, and few are listening.

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3. *Post-Infectious Neuromyasthenia (Chronic Fatigue Syndrome): A Summary of Ongoing Studies*

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A Summary of Ongoing Studies

Chronic fatigue syndrome (CFS) is the most recently accepted term in North America for an illness that is also known by a variety of other names, including myalgic encephalomyelitis[1], chronic mononucleosis[2], post-viral asthenia[3], post-viral fatigue syndrome[4], chronic Epstein-Barr virus (CEBV) infection [5,6], and post-infectious neuromyasthenia (PIN)[7]. It is also known by a number of names that have been applied to specific epidemics, such as Royal Free disease[8]. Although the illness has been linked with the Epstein-Barr virus (EBV), we have maintained that an identical illness occurs after a variety of other infections[7]. We, therefore, found the term CEBV to be inappropriate and have, since 1984, used the more general term, post-infectious neuromyasthenia. The term "post-infectious" was used because most cases occurred after a documented or suspected acute infection, but it is clear that a significant proportion of patients do not appear to have the onset of their illness with an apparent acute infection. The term "neuromyasthenia" (or neurasthenia) was used to indicate that the patients had fatigue and subjective weakness without objective findings. These symptoms have been designated as neurasthenia or neuromyasthenia to describe episodes of endemic and epidemic disease for over 100 years[9,10]. Those who originally felt that this was a chronic EBV infection[5] subsequently agreed with us that this was, in most cases, not clearly the triggering event; in 1988 the more noncommittal term, chronic fatigue syndrome, was then selected to define the illness[11]. Post-infectious neuromyasthenia is identical to CFS except that we had the requirement for an apparent acute infection at the onset and we did not include as criteria the few abnormal physical findings which are part of the CFS definition.

CFS is a topic of great interest because of its significant prevalence, degree of occupational and social dysfunction, emotional distress, and the significant costs to society. There has been much debate as to the pathogenesis of this illness because patients exhibit both physical and psychologic symptoms. One etiologic agent after another has been proposed as the cause of CFS but the evidence remains that there is no one agent that results in this syndrome[7]. The problem is compounded by the absence of rigid diagnostic criteria, which may mean that we are dealing with a syndrome potentially caused by a variety of different agents or which is a collection of different diseases. Those who attempt to understand this condition have been polarized into one of two camps: those who espouse the purely organic theory and those who feel that this is an emotional ailment.

We have done some studies on various aspects of CFS in order to provide some further understanding of this condition. We outline some of the studies below and utilize these results to provide a hypothetical framework for the pathogenesis of CFS as well as a suggested approach to managing patients with this problem.

Causative Agents

The EBV has been recently popularized as the causative agent of CFS[5,6]. Because of this, we have looked for an increased prevalence of EBV pharyngeal excretion in CFS patients compared to normal controls. There was no evidence for an increased viral excretion in the CFS group and there seems to be little evidence for EBV reactivation in this group. A small minority of patients do, however, develop CFS after a definite bout of acute infectious mononucleosis. Chronic fatigue syndrome, however, is clearly associated with many other defined infections. We have documented that it occurs after giardiasis, genital herpes infection, coxsackie infection, influenza, and mycoplasma pneumonia[7]. It is unlikely that there will be any one causative agent found. It is more likely that a variety of infections may trigger CFS by activating some common mechanism, possibly related to the immune system.

Immunologic Abnormalities

The immune system has been the subject of investigation in CFS because initially it was felt that the patients had a chronic EBV infection which they could not eliminate and because many patients state that they seem to get repeated flu-like illnesses. Indeed, immunologic studies have indicated the following abnormalities: increased T4:T8 cell ratios, decreased natural killer cell activity, decreased *in vitro* interferon gamma production, diminished interleukin-2 production, decreased *in vitro* antibody synthesis following mitogen stimulation, and circulating immune complexes[12]. In our investigations, we have found several consistent immunologic abnormalities. Almost one-half of the patients have a modest elevation of 2-5A oligo-adenylate synthetase, which is an interferon-associated enzyme commonly elevated in acute or chronic viral infection such as human immunodeficiency virus (HIV) infection. The levels of synthetase are generally lower than those which are found in acquired immunodeficiency disease syndrome (AIDS). There are also frequent abnormalities in total levels of immunoglobulin classes; the most frequent abnormalities include elevated Immunoglobulin M(IgM) and depressed IgA. The third change which we have noted is a very mild reduction in C4. We have also studied the reactivity of peripheral blood lymphocytes to 5 different antigens in these patients and we have found that 30-40% of patients have a definitely diminished response to at least 2 out of the 5 tested antigens. Lastly, we have looked for the presence of antibodies to DNA by enzyme-linked immunoabsorbent assay (ELISA): 40% of patients with CFS have elevated antibodies to single-stranded DNA but it is rare for there to be antibodies to double-stranded DNA.

It is clear that some immunologic abnormalities are detectable in a

minority of patients with CFS. The significance of these findings is uncertain because most of the changes are mild, do not exist in all of the patients with CFS, do not clearly correlate with the clinical status, and have not been rigorously compared to appropriate control groups.

Sleep Physiology

Patients with CFS complain of one or more of the following sleep disturbances. They may awaken frequently during the night, and, especially at the onset of their illness, many patients sleep for an excessive number of hours compared to their pre-morbid sleep pattern. One previous report has described physiologic evidence for mild hypersomnolence in patients after infectious mononucleosis[13]. Generally, however, the hallmark of this condition is that CFS patients suffer from non-restorative sleep, which means that their tiredness remains when they awaken in the morning or it follows again very shortly after reawakening.

We systematically investigated 14 patients with CFS and 11 healthy controls by administering questionnaires which included a sleep-wake questionnaire and by testing the patients in the sleep laboratory for 3 consecutive nights with clinical polysomnography[14]. Polysomnography consisted of continuous overnight monitoring of electroencephalography (EEG), electrooculography, electrocardiography, and electromyography of the sub-mentalis. The results of the study showed decreased sleep efficiency, a delayed onset of the consolidated stage of sleep, diminished percentage time in rapid eye movement (REM) sleep, and greater alpha EEG activity during non-REM sleep. Although most patients claimed that they required more sleep since the onset of their illness, sleep studies showed no physiologic evidence for nocturnal or daytime hypersomnolence. Alpha EEG sleep has been interpreted as evidence for an EEG arousal disturbance in non-REM sleep and has been associated with the fibrositis symptoms of widespread musculoskeletal pain, chronic dysphoria, and fatigue. The sleep physiology seen in the patient group was, however, quite unlike that seen in dysthymic disorder or in major depressive disorder. This study demonstrates the overlap between the fibrositis syndrome and CFS. Many of the patients with CFS who were analyzed in this study did have fibrositis-tender points and other studies with fibrositic patients have shown that they have symptoms commonly seen in CFS[15].

Radionuclide Brain Scanning

Brain imaging was carried out consecutively on 43 CFS patients. The type of scan which was done involved injection of hexamethylpropylene amineoxime (HMPAO) and this was followed by imaging using a form of computerized tomography known as SPECT. Twenty-six (61%) of the 43 patients demonstrated an abnormal pattern; this predominantly consisted of diminished uptake in 1 or both basal ganglia in 21/26 (81%). Diminished uptake was also seen in the frontal (6/26 [23%]), temporal (2/26 [8%]), or parietal lobes (2/26 [8%]). Of the 21 patients with abnormal basal ganglion uptake, 15/21 (71%) had these basal ganglia abnormalities only and 6/21 (29%) had mixed defects. The significance of this type of abnormal uptake is unknown but similar changes have been noted in brain scans done on patients with affective disorders.

Cognitive Impairment

A very common complaint of patients with CFS is an inability to concentrate on tasks. Furthermore, many patients have complaints of short-term memory impairment, dyslogia as well as paralogia. These are disabling symptoms particularly for patients who must speak in public and those who are in positions of responsibility. It is in part for the above reasons that many patients cannot continue working; they feel that they are unable to perform as they did previously.

In order to assess the apparent cognitive impairment, we studied 21 CFS patients by using 5 different psychometric tests[16]. Surprisingly, the CFS group performed at a significantly higher level in comparison with the normative controls on almost all of the tests. It is important to note that, during the testing, the participants felt that they were performing quite poorly. It is entirely possible that the patients were indeed performing at a level that did not meet their usual standards. Despite this possibility, the patients' level of disability still seemed to be out of proportion to the objective findings on these tests.

One interpretation of these findings is that the patients do not have an organic (neurologic) abnormality; rather, their disability is due to other factors such as emotional difficulties or extreme (mental) fatigue which is exacerbated when they are stressed. The cognitive impairment may be due to specific situational stresses. Some evidence for the latter is provided by the observation that many patients do not have severe cognitive impairment under low-stress circumstances but are impaired in other circumstances, such as inside their area of employment.

Psychologic Studies

Most CFS patients have what are considered to be psychologic symptoms and, in particular, they have depressive symptoms. This has been evident from a structured questionnaire which we have administered to all of our patients; a majority of the patients have 1 or more of the following complaints: frequent crying spells, emotional lability, feelings of loneliness, blue periods, feelings that others are unsympathetic, and fear that there is something seriously wrong with their bodies. In the case definition of CFS, one of the exclusion criteria is "chronic psychiatric disease, either newly diagnosed or by history." This is a contentious issue because I believe that most patients with CFS do, in fact, have psychologic symptoms and, as will be noted below, if one probes carefully enough there may be a past history of psychiatric abnormalities. Chronic, pre-existent, and obvious psychiatric abnormalities that have interfered with function should be part of the exclusion criteria. It is not clear that others should be excluded.

We initiated one of the first systematic studies into the psychiatric abnormalities present in patients with CFS[17]. Twenty-four CFS and a similar number of control patients were studied using a structured interview, the Beck depression inventory (BDI), as well as a dexamethasone suppression test. Seventeen of the 24 patients (71%) were found to have affective disorders and 16 of these 17 had major depression. This was significantly different from the controls but the controls and patients did

not differ in the frequency of anxiety disorders or disorders of substance abuse. According to the BDI score, 5 of the 16 depressed patients had only mild depression but the remaining 11 had more severe depression with BDI scores of >16. A dexamethasone suppression test was administered to 16 of the patients and all but 2 were normal responders. It was of great interest to note that 12 of the 24 patients in fact had at least 1 major depressive episode *before* the onset of CFS. These findings suggested that there was depression during CFS; this may have been precipitated by an acute infective event occurring in patients who were psychologically predisposed.

Studies of the Royal Free epidemic have suggested that the episode was one of "mass hysteria"[18] and that the affected nurses had higher neuroticism scores. Subsequent studies have confirmed the higher prevalence of depressive symptoms in CFS[19,20,21]. Other psychiatric disorders including somatization also seem to be over-represented in CFS patients[19].

Wessely (1989) compared CFS patients to those with neuromuscular diseases and those with major depression. Mental fatigue was similar in the post-viral and the affective disorder groups but was greater than in the neuromuscular group. Major depression was found in almost one-half of the post-viral fatigue group, which was significantly higher than the neuromuscular controls.

There are a number of different possible explanations for the prominence of depressive symptoms in CFS: (1) the findings are spurious and result from the symptoms of CFS mimicking those of major depression; (2) an organic mood disorder results from the underlying pathophysiologic insult (e.g., viral or toxic agent); (3) the mood disorder is an adjustment reaction to the disability associated with CFS; or (4) a major depressive syndrome is really the primary pathology at the root of CFS.

Major Stress Factors

We have studied the presence of stress factors just prior to the onset of CFS in patients with the syndrome and in controls. We have found that almost all of the CFS patients have had 1 or more stressful events in the 6 months prior to the onset of their illness. Only 5% of healthy controls had a history of similar stresses. Some very common events included the starting of a new job, preparation for an upcoming marriage, major problems with a relationship, or serious illness in the family.

Hypotheses

Any hypothesis to explain how CFS occurs obviously must incorporate the accepted findings from previous studies. It is proposed that the disease occurs in the following fashion. There is a coterie of susceptible patients in the population. These are subjects who have had major depressive episodes in the past and who are potentially susceptible to major depressive episodes in the future. This group of patients is then exposed to 1 or more major stressful events as noted above. Under the circumstances, they may become particularly susceptible to acute infections and to the more chronic symptoms of the disease. In response to an acute infective episode which may have affected other family members and friends, the patient does not fully recover, whereas other family members quickly recover. The combination of sleep disorder and psychologic symptoms culminates in daytime fatigue which interferes with work. The mild immunodeficiency in some cases may result in recurrent flu-like illnesses which compound the fatigue, and the cycle continues.

Some patients may enter this cycle at the point of the infection, some may enter when they develop major depression, and some may enter because they have a sleep disorder, perhaps related to muscle aching (fibrositis syndrome).

Managing CFS Patients

Although there is no single approach to CFS patients that has been shown to have great utility, we believe that an appreciation of the above abnormalities and use of the above hypothesis can help most patients improve. Specifically, patients must appreciate that psychologic symptoms are present, that there have been stress-related factors just prior to the onset of their illness, and that they must try to avoid such stresses. The prominent symptoms, such as the sleep disorder, anxiety, or depression, must be treated and not ignored irrespective of the etiology. Making the assumption that this illness is *either* organic *or* psychiatric renders a disservice to the patient. One must appreciate the contribution of *both* organic and psychiatric factors in the generation of this devastating illness.

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4. *The Psychiatrist and Chronic Fatigue Syndrome*

R.G. Cooke

Unlike the rest of the participants, I don't work directly with chronic fatigue syndrome (CFS), but rather with the following psychiatric conditions: major depression and manic-depressive (bipolar) disorder. Together these are known as the major affective or mood disorders. I intend to discuss the possible relationship between these illnesses and CFS, in part to alert physicians to the importance of considering these usually treatable psychiatric conditions in the differential diagnosis of chronic fatigue. I will briefly recap the salient features of the mood disorders, discuss the striking similarities (possibly superficial) between major depression and CFS, and finally deal briefly with the psychiatric aspects of CFS.

The affective disorders are episodic and/or chronic psychiatric disorders characterized by disturbances primarily in mood, but also in energy, thinking, and behavior. The term "major depression" refers to an illness involving recurrent depressive episodes, while bipolar (manic-depressive) disorder is characterized by episodes of mania (elevated mood) with or without interspersed depressive episodes. The cause(s) of these mood disorders are not known, but the possibility of a biologic etiology is supported by data from genetic, pharmacologic, biochemical, and other studies. Popular etiologic theories implicate alterations in neurotransmitter function, involving noradrenergic, serotonergic, and/or cholinergic systems, in the pathophysiology of these illnesses. The biologic etiology is also supported by the "endogenous" nature of these disorders, i.e., they can occur or recur in psychologically well-adjusted persons. However, psychosocial factors do appear to contribute to the etiology and/or presentation of mood disorders as well. (The reader is referred to any general textbook of psychiatry for a further discussion of these issues.)

Table 1.
Similarities between Major Depressive Disorder and Chronic Fatigue Syndrome

(Sources are cited in reference 13)

Demographics:	Age
	Sex
	SES*
Symptoms:	Depressed mood
	Fatigue
	Malaise
	Headache
	Cognitive impairment: Concentration memory
Course:	Chronic/Recurrent
	Onset following "Flu" or EBV infection*
Laboratory Findings:	Hypogammaglobulinemia
	NK cell function or numbers
	Abnormal lymphocyte mitogen responses
	Interferon
	Autoantibodies
	Viral Antibodies
Associated Illness:	Thyroiditis*
	Allergies
Response to Treatment:	Antidepressants
	Other

* Indicates weak or anecdotal evidence

Estimates of the prevalence and incidence of the affective disorders vary, but a recent report from a large-scale Canadian study[1] estimated an annual incidence rate for depression of 2.3/1000 and a prevalence rate of 5.6/100, making depression one of the commonest of all medical disorders. Manic-depressive (bipolar) disorder afflicts about 1% of the population[2]. Affective disorders are also said to account for as many as 20-25% of visits to general practitioners[3]. The onset of the disorders can occur at any time of life, but quite often occurs in the third or fourth decade, with bipolar disorder coming on a bit earlier. Drugs and electroconvulsive therapy have been the mainstay treatments for mood disorders for several decades, and accumulating evidence also demonstrates a role for 2 forms of psychotherapy, interpersonal therapy and cognitive therapy, in the treatment and prevention of major depression[4,5]. However, several reports have indicated that a high proportion of patients exhibit chronic (>1 year) or frequently recurrent episodes despite access to health- care facilities[6-9]. This discouraging outcome may largely reflect underdiagnosis and undertreatment of mood disorders, both in the community and in academic centres[3,9,10-12].

Let me now discuss the many, possibly superficial similarities between major depression and CFS (Table 1). (For more detailed discussion and references, see reference 13.) The age of onset for both depression and CFS is often in the twenties or thirties, and in both illnesses there is a predominance of female cases. Both have been tentatively linked to higher socioeconomic status, although for both this may be misleading; better-educated or wealthier patients may have better access to physicians or a lower tolerance for disability, leading to a greater likelihood of seeking help for chronic symptoms. In terms of the symptom picture there are many similarities between major depression and CFS (Table 1). Regarding the cognitive symptoms, there are some anecdotal reports that

neuropsychologic test results differ between CFS and depressed patients, but I haven't seen the data. Both the mood disorders and CFS can run a chronic or recurrent course. The relationship of CFS to flu-like illnesses and, in some cases, to Epstein-Barr virus (EBV) infection is well known to you. Anecdotally, patients with major depression often report an onset following flu-like symptoms, and this seems to be specific to depressive disorders compared to other psychiatric conditions such as schizophrenia. There is also a handful of case reports of depressive or manic symptoms occurring after infectious mononucleosis (i.e., acute EBV infection). Laboratory findings that have been reported in common between major depression and CFS (Table 1) are all very mild or have been inconsistently reported. I would like to dwell on the last one (viral antibodies) for a moment. Chronic fatigue syndrome was formerly referred to as chronic EBV (CEBV) syndrome and a number of reports suggest that these patients have elevated antibodies to EBV, even though an etiologic role for the virus has now been pretty well dismissed. There have also been several controlled studies that reported altered EBV antibody profiles in patients with mood disorders compared to controls. In fact, for both major depression and CFS, antibodies to several viruses seem to be mildly elevated, and the general consensus is that this is probably a result rather than a cause of the syndromes. There are anecdotal comments in the literature (but very little data) suggesting that CFS patients may respond to antidepressants, or to nifedipine or ranitidine, which have both been tried in depressed patients with some success in case reports.

Basically, then, there are many superficial similarities between major depression and CFS (and there may be many differences on which I didn't comment). Next, there are actual psychiatric studies that have been carried out on CFS patients. Straus and colleagues[14] reported that 8 of 11 "CEBV" patients assessed by a psychiatrist were given psychiatric diagnoses, including somatization disorder, anxiety disorder, and depression. Apparently because the authors were convinced at that time that their patients were suffering from CEBV infection, they didn't pay too much attention to the psychiatric findings. The first systematic study was done by Dr. Salit in association with Taerk and others[15]. After administering a standardized psychiatric diagnostic interview (the DIS) to patients whom Salit had diagnosed as suffering from sporadic post-infectious neuromyasthenia, i.e., CFS, they found that 67% of patients met the American Psychiatric Association DSM III criteria (since revised to DSM-III-R)[16] for major depressive disorder. Because the symptoms of neuromyasthenia and depression were similar, this might indicate some false-positive depression diagnoses. However, 50% of the patients had evidence of major depressive episodes before the neuromyasthenia, and the false-positive notion does not seem to apply for those patients. This study was recently replicated by Kruesi and colleagues[17] who found that 75% of a group of patients who met the Centers for Disease Control (CDC) working case definition for CFS[18] had a psychiatric diagnosis by DIS interview, including 46% with major depressive disorder. These authors used a very conservative interpretation of the DIS: symptoms attributable to CFS were not counted toward a psychiatric diagnosis. Like Taerk and associates, they also reported that depression frequently preceded CFS.

These studies suggest that CFS is very similar to major depression, and often occurs in people with a history of depression. Thus, the 2 conditions are difficult to distinguish. Comparing the CDC criteria for CFS with the DSM-III-R criteria for major depression, the main distinguishing factor seems to be the requirement of pharyngitis, adenopathy, and fever documented on at least 2 occasions 1 month apart in CFS patients. However, this may simply reflect the intention of the CDC team to confine the diagnosis of CFS to a hard-core group of patients with physical findings. In the earlier literature on so-called CEBV, many of the writers emphasized that physical findings were transient or infrequent in their patients. Furthermore, pharyngitis, fever, and adenopathy could conceivably occur every couple of months in many patients with affective disorders as a result of common upper respiratory infections. In the end, both CFS and major depression are diagnosed by very similar criteria, and in the absence of any definitive laboratory tests or established etiology for either condition, we can't clearly delineate them from each other.

Assuming that CFS is indeed distinct from major depression and is an organic illness due to some unknown factor such as a viral infection, why is there a common finding of a history of previous depression in persons with CFS? A number of investigators have commented on this, and have suggested that psychologic factors may contribute to the development of CFS. While this is an attractive notion, it is equally plausible that the psychiatric disorder may predispose to CFS through biologic mechanisms. For example, a disturbance in noradrenergic neurotransmission is postulated in depression, and noradrenaline is also known to be important in regulating the immune system[19]. Therefore, one could argue that patients with depression are vulnerable to reactivated or poorly resolving viral infections leading to CFS as a result of defective noradrenergic function, without invoking any role for psychologic factors.

As for the psychiatric aspects of CFS, what can a psychiatrist do for these patients? The short answer is I don't know. The literature on CFS suggests that psychotherapy, supportive counselling, and education are important for these patients, and that antidepressant medication may be helpful. However, there has been little or no study of these interventions in CFS patients, and clearly this type of research is much needed. Since the evidence suggests a role for cognitive therapy and interpersonal therapy in the treatment and relapse prevention of depression, these types of psychotherapy should be studied in CFS patients. Antidepressant medications must also be studied in CFS patients, and should even now be considered for CFS patients who also meet the criteria for major depression.

In closing I would like to mention the study by Manu and colleagues[20] of a series of patients referred to a fatigue clinic with self- or physician-diagnosed chronic fatigue. Forty-three percent of these patients were eventually diagnosed as having a major depression, while only 4% were diagnosed as having CFS. This

emphasizes, for physicians in general practice, the importance of recognizing the high likelihood of major depression in patients with chronic fatigue.

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5. *Clinical Observations of Chronic Fatigue Syndrome*

C.A. Mildon

Introduction

Like that of many physicians, our practice saw about 2 cases per year of post-viral neuromyasthenia. However, in February 1982, after 11 years of medical practice, we began to see many more patients with these signs and symptoms, which were lasting longer than expected. Moreover, the patient load was in an unusual age range, being predominantly in the thirties and forties.

The appearance of this disease seemed to be similar to acute or subacute mononucleosis which had lingered longer than usual. However, some of the acute symptoms of acute mononucleosis seemed to be missing from this clinical syndrome.

Clinical Observations from February 1982 to August 1983

The symptoms of this particular group of patients included excessive fatigue; extreme muscle weakness, both symptomatic and objective in many cases; a recurrent sore throat and ears; and discomfort or pain in the lymph nodes, liver, and spleen. There was also disturbed GI function in most of the patients. Most of the patients had enlarged and tender lymph nodes, although some had enlarged lymph nodes only. Most of them had low-grade fever ranging up to 37.6 °C. Many of them also had tender kidneys to the punch and palpation, and one of the common complications besides bronchial disease and pneumonitis was acute or subacute pyelonephritis.

Change of Opinion

In August 1983 it became apparent that the disease being observed was not acute mononucleosis, partly because the age of the patient load was over 30 and partly because many of the distinctive symptoms of acute mononucleosis due to Epstein-Barr virus (EBV) were absent. Although at this time we were beginning to see many cases with positive viral capsid antigen (VCA) 1:640 or greater and early antigen (EA) 1:40 or greater, nevertheless, it became apparent that the disease was probably not Epstein-Barr mononucleosis.

What was remarkable was that most of the patients took much longer than 6 months to recover from the malaise and weakness of their disease. At this time the sex ratio of the group seeking medical attention in the office was female:male, 2:1.

Stages of Disease for Diagnostic Purposes

It is of much greater help to the physician in general practice or in the office to observe that the guidelines for diagnosing chronic fatigue syndrome (CFS) are different in different stages of the disease. As in most diseases, there is a natural progression to the disease and diagnosis may take place at any time during the course of the disease along that continuum.

Stage One

The characteristics of this stage include severe hypersomnia, greater than 10 hours per day. Usually the patient sleeps this length of time in 1 block with other naps during the day. However, some patients may actually sleep in segments throughout the 24 hours. There is a sense of profound weakness. The clinician observer may see recurrent acute infections both in the lungs and kidneys. However, the recurrent laboratory changes are minor.

Stage Two

During this stage, which takes place about a year to a year and a half after the first stage, the patient begins to want prolonged rest periods, about 12 hours per day, but less actual sleep is needed. There is muscle weakness plus aching, subjectively. In at least 50-67% of the patients, tenderness of the muscles will be felt upon palpation. There are fewer acute infections, although some infections become chronic. This is particularly true in the case of the kidneys.

What is perplexing is that, as the clinician observer encourages the patient to undertake the healthy measures of exercise, social life, and diet in a healthy mode, in actual fact the patient may feel worse, with worse signs and symptoms. However, the patient should be encouraged to continue these 3 modes of rehabilitation, moving as slowly as absolutely necessary to maintain strength and the ability to sleep and participate in family life.

Stage Three

Here, the patient shows a great deal of restlessness and, when the patient does sleep, the sleep appears to be non-restorative in many cases. Many patients develop rheumatic and arthritic changes, with 40% of the women over 40 years of age developing fibromyositis. It should be noted that about 10% of male patients will develop this disease and are usually in a younger age group, approximately 33 to 36 years of age.

The patient will very likely show a pattern of alternating "good and bad days," with the pattern evolving that the good days last longer and longer and the bad days become paler versions of the past.

Intermittently, sometimes once a month, sometimes more often, and occasionally only every few months, the patient will undergo a mild version of the original attack, feeling flu-like, having tender enlarged lymph nodes, and going through a repeat of the symptoms that were experienced in the first stage. However, this relapse is usually over in a short period of 3 to 5 days or, at most, about 10 days.

This last stage usually takes place in the third year of the disease in a patient who is getting better after 3 to 5 years, or it may actually take place after many years of chronic illness.

It should be noted that many patients have non-stop, unrelenting illness. It has been our experience after seeing over 700 patients that usually those patients who smoke on a regular basis, particularly those who smoke a package of cigarettes a day, are the ones who have the worst chronic inflammation pattern and will suffer almost steadily day-by-day over a number of years.

Exclusion Criteria

1. We exclude all patients who overuse alcohol — by which we mean 3 oz. of liquor per week or 3 wine or 3 beers per week. This is because alcohol intolerance is one of the hallmarks of this disease among almost all patients. Consequently, any patient who can tolerate a great deal of alcohol in the course of normal living is unlikely to have CFS and immune dysfunction syndrome. Sometimes these factors can be excluded but it is very unlikely. Tenderness of the muscles in these patients should be considered to be due to secondary alcoholic myopathy rather than to the CFS.
2. All other diseases should be ruled out. However, a clinician who has seen scores or hundreds of cases of CFS might be able to bend this rule a bit.
3. It is very important to rule out malignant hyperthermia in these patients. Chronic fatigue patients display very similar symptoms to those of this rare disease. Malignant hyperthermia is **life-threatening** and no other disease considered for exclusion in the chronic fatigue-presenting patient is life-threatening. Therefore, it is extremely important that all clinicians and observers rule out malignant hyperthermia by measuring creatine phosphokinase (CPK) and CPK isoenzymes. Should the skeletal muscle component (CPK3[MM]) prove to be dominant and abnormal in the isoenzymes and should the CPK be elevated above normal, the patient should be considered to have malignant hyperthermia and should be immediately referred to a recognized investigator or authority in this disease. Not only does the life of this patient depend on accurate diagnosis but so do the lives of many of his/her near relatives. No other diagnosis is so important in the differential diagnosis of CFS and immune dysfunction syndrome.

Prognosis

It must be emphasized here how very approximate prognosis can be in these chronic fatigue patients. Usually, the prognosis is related to the age of the patient at the time of onset and the severity of the disease in the early stages and later, as well as to some extent to the amount of social and psychologic support the individual patient has in his/her personal life.

We have found the following limits of prognoses to be fairly reliable:

1. Age 10-30 years: 18 months to 2 years
2. Age 30-40 years: 2 to 3.5 years
3. Age 40-65 years: 3.5 to 5 years
4. > 65 years: 2-3 years

These figures are only approximations because we have seen 18-year-old patients ill for 3 and 4 years whereas a 55-year-old patient was sick for only 9 months. It is possible, when all other factors are ruled out, to diagnose this disease right up the early seventies in some vigorous, healthy older patients.

Treatment

Exercise

There is a great deal of controversy as to exercise, from some specialists advocating aerobic exercise to the more general British tendency to advocate complete rest. However, evidence has shown that there is a defect in the muscular cell of these patients and possibly some benefit can be had from very mild to moderate regular exercise. This will have to be left to the individual patient, as excessive motion and exercise will aggravate the lactic acid defect in the muscle cell and can result in bed rest of a minimum of 3 to 5 days, duration with nothing gained from this excessive exercise. Sometimes, exercise involves simply walking out of the house to the corner of the street and back to the house again. It is impossible to emphasize enough to the clinician that a small amount of exercise in these patients goes a long way. Apparently, increasing the load on the muscle cell will work somewhat to benefit the patients, especially those who have entered into the chronic stage of fibromyositis.

Diet

By trial and error it has been found that a low-fat diet which is also high in vegetables, low in fruits, and moderate in meat and cereals has been greatly beneficial to these patients, especially those with the musculoskeletal defect that is causing them impairment of motion and a great deal of pain.

Rest

It cannot be emphasized enough how much rest is ultimately the best mode of repair for these patients. By the third stage of the disease they will not sleep as much but they will definitely need to rest, usually in the supine position, and they can usually do little reading due to transient vision defects. A balance between exercise, diet, and rest should be encouraged in these patients and when the disease worsens they should be immediately encouraged to return to rest for a few days until they are able to get on with their normal life.

New Therapies Appearing on the Scene

Through trial and error existing therapies are being adapted specifically for treating CFS, and we are beginning to implement them in Eastern Canada.

Tonics

There are several tonics on the market which, surprisingly, are extremely beneficial to these patients, especially those who have recurrent liver enzyme elevation and chronic problems with the gastrointestinal tract. They are also beneficial for muscle pain and dysfunction.

Electromagnetic Therapy

Very low frequency (2 to 30 Hertz) electromagnetic therapy can be used for residual musculoskeletal pain and dysfunction. For those with fibromyositis this therapy seems to relieve the pain. With minimal follow-up painlessness can be maintained.

Massage Therapy

It has become apparent that massage therapy of the Swedish type helps tremendously in alleviating the pain and discomfort of these patients. They also sleep better. This is not because it makes them feel good, although this takes place as well; rather, research has shown that regular, even, rhythmical massage over a period of 30 minutes to an hour allows

the body to enter into the parasympathetic mode, causing repair of some of the tissues and relaxation. Patients should be encouraged to sleep or rest for 1 to 2 hours following massage therapy.

Finale

Whatever the future holds, we expect that a physiologic basis will be found for CFS.

6. *Summary — Session A*

K. Rozee

Summary

Dr. Joncas introduced the subject of chronic fatigue syndrome (CFS) by suggesting that consideration be given to the hypothesis that, instead of CFS being a post-viral-infection syndrome, as appears to be the consensus, it be considered primarily a metabolic disorder either inducing usually latent infections or induced by these infections.

This paper was followed by an historical summary by Dr. Hyde leading to a proposal that polioviruses be reconsidered as a causal factor in CFS.

Dr. Salit and co-workers have provided an overview of their extensive medical experience with patients with this syndrome. They make the suggestion that the patients' psychologic state, stress, infectious events, and clinically measurable sleep disorders all may play a role in the evolution of CFS. These, they suggest, may allow patients to initiate CFS at various points in a cyclic series of events, i.e., depression, depressed immunity, infection, sleep disorder, fatigue leading to depression, etc.

Dr. Cooke discussed the similarities and differences between CFS and major depression, one of the common effective disorders of psychiatry. Similarities are many: age of onset, episodic character, excess of female cases, and even high levels of antiviral Epstein-Barr virus (EBV) antibodies, but they also have some apparently defining differences, particularly a prior history of major affective disorders, although the differentiation is quite difficult in objective terms. What is perhaps important is the observation that a high percentage of CFS patients are found to suffer from major depression, and suggestions are common that these would benefit from supportive psychiatric help.

This session was closed by Dr. Mildon who described her experiences as a physician with many CFS patients under treatment. She concluded that her patients' illnesses could be grouped into 3 phases progressing slowly over several years. She suggested that the clinician should be alert to exclusion factors such as alcohol overindulgence or malignant hyperthermia. With respect to recovery and treatment, Dr. Mildon suggested that very conservative exercise, low-fat diets, and much rest are important features and, even then, recuperation requires several years at best.

Session B
Possible Etiologies and Therapeutic Interventions

7. *Chronic Fatigue Syndromes: A Preliminary Overview*

A.L. Komaroff

Practising physicians frequently see patients seeking care for the complaint of chronic fatigue. Most of the time, formal or informal evaluation leads to the conclusion that the patient is depressed, or anxious, or both. On unusual occasions, the patient may be suffering from a well-recognized "physical" disease such as an occult malignancy or thyroid disease.

Yet another subgroup of patients with chronic fatigue, presumably a small fraction, do not fit the pattern of any recognized physical disease, but do have features that suggest an "organic" disorder. Over the past 100 years, the medical literature has included descriptions of several ill-defined clinical syndromes that produce chronic fatigue. In recent years, there has been much speculation that these syndromes may be secondary to chronic viral infection. The syndromes go by different names, but share so many clinical and laboratory features that some believe they may be the same illness, that is, they may share a final common pathogenetic pathway.

Neurasthenia (or neurocirculatory asthenia) was first described in the mid-19th century[1]. Typically an affliction of young adults, usually women, the illness often starts with an acute infectious illness. In the early 20th century, the illness was ascribed to "weakness" of the nervous system and cardiovascular system, but no characteristic objective deficits were identified. For that reason, the diagnostic label lost favor, and has been rarely used in the medical literature of the past 40 years.

True chronic mononucleosis[2-4] starts with classical acute infectious mononucleosis, as characterized by clinical, hematologic, and serologic features. However, instead of recovering, these patients remain ill for years. Some (but not all) have serologic evidence of persistently active Epstein-Barr virus (EBV) infection.

Severe chronic active EBV infection is a chronic illness that sometimes (but not always) follows acute infectious mononucleosis[5,6]. Patients all have strikingly abnormal serologic studies (EBV-VCA-IgG greater than or equal to 1:5120; or early antigen-Ab greater than or equal to 1:320). These patients often have evidence of major organ involvement, such as recurrent interstitial pneumonia, persistent non-A or non-B hepatitis, splenomegaly and adenopathy, pancytopenia, or selective cytopenia. Most observers assume that these patients have an illness related to EBV infection, in which immunologic containment of EBV is impaired.

Myalgic encephalomyelitis (also called epidemic neurasthenia, Icelandic disease, Royal Free disease) is similar in most respects to the other chronic fatigue syndromes. What is apparently different about these patients is that their illness typically begins as part of an "outbreak": multiple members of a small community or co-workers in a large institution become ill within a relatively short period of time with a similar illness. Over 30 outbreaks of myalgic encephalomyelitis have been reported in the medical literature[7,8].

Fibromyalgia or fibrositis is another similar illness[9,10]. The diagnostic label is used most commonly by rheumatologists, because of the predominance of painful muscles and painful joints. However, patients with fibromyalgia are virtually all chronically fatigued, and for many the fatigue is the most debilitating symptom of their illness. Moreover, patients with fibromyalgia also often have features seen in chronic fatigue syndrome (CFS): sudden onset of the chronic illness with an acute, apparently infectious illness, chronic fevers, adenopathy, and cough[11].

Chronic Fatigue Syndrome (CFS)

In 1988, a group of investigators, under the leadership of the United States Centers for Disease Control, developed a working case definition of an illness called chronic fatigue syndrome[12]. This case definition is summarized in Table 1. The definition relies entirely on a combination of symptoms and signs (not laboratory data), and on the exclusion of chronic active "physical" or psychiatric illnesses that can produce chronic fatigue.

The working case definition is only now being tested in practice. It is not yet clear whether the current case definition accomplishes the objectives of any case definition: the identification of a group of individuals with a common and characteristic pathologic abnormality and/or a common and characteristic prognosis.

We have been studying a group of 350 patients over the past 3 years. All of them have been ill for at least 6 months. Most of them fully meet the working case definition of CFS. Those who do not fully meet the case definition are otherwise indistinguishable from those who do[13]. The findings in our group (which have not yet been published in detail) closely parallel those reported previously by others[14-16].

The average patient is 37 years old, but the age at onset ranges from 11 years to 60 years. Approximately 70% of the patients are women. The patients generally are middle class, but all socioeconomic groups are represented. The main symptom is fatigue. In our studies, the typical patient has been ill for over 3 years, and remains ill as of the time of this submission. Approximately 25% describe themselves as regularly bedridden or shut-in, unable to work. Approximately one-third can work only part-time. Before they became ill, the patients perceived that they typically were more energetic than most of their friends.

Table 1.
A Working Case Definition of Chronic Fatigue Syndrome*

A case of chronic fatigue syndrome (CFS) must fulfill major criteria 1 and 2, and the following minor criteria: 6 or more of the 11 symptom criteria and 2 or more of the 3 physical criteria; or 8 or more of the 11 symptom criteria.

Major Criteria

1. New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, that does not resolve with bed rest, and that is severe enough to produce or impair average daily activity below 50% of the patient's pre-morbid activity level, for a period of at least 6 months.

2. Other clinical conditions that may produce similar symptoms must be excluded by thorough evaluation, based on history, physical examination, and appropriate laboratory findings. These conditions include malignancy; autoimmune disease; localized infection (such as occult abscess); chronic or subacute bacterial disease (such as endocarditis, Lyme disease, or tuberculosis), fungal disease (such as histoplasmosis, blastomycosis, or coccidioidomycosis), and parasitic disease (such as toxoplasmosis, amebiasis, giardiasis, or helminthic infestation); disease related to human immunodeficiency virus (HIV) infection; chronic psychiatric disease, either newly diagnosed by history (such as endogenous depression, hysterical personality disorder, anxiety neurosis, schizophrenia) or by chronic use of major tranquilizers, lithium, or antidepressive medications; chronic inflammatory disease (such as sarcoidosis, Wegener's granulomatosis, or chronic hepatitis); neuromuscular disease (such as multiple sclerosis or myasthenia gravis); endocrine disease (such as hypothyroidism, Addison's disease, Cushing's syndrome, or diabetes mellitus); drug dependency or abuse (such as alcohol, controlled prescription drugs, or illicit drugs); side effects of a chronic medication or other toxic agent (such as a chemical solvent, pesticide, or heavy metal); or other known or defined chronic pulmonary, cardiac, gastrointestinal, hepatic, renal, or hematologic disease.

Minor Criteria

To fulfill a symptom criterion, a symptom must have begun at or after the time of onset of increased fatigability, and must have persisted or recurred over a period of at least 6 months (individual symptoms may or may not have occurred simultaneously). Symptoms include:

1. Mild fever – oral temperature between 37.5 °C and 38.6 °C, if measured by the patient – or chills. (Note: oral temperatures of greater than 38.6 °C are less compatible with CFS and should prompt studies for other causes of illness.)

2. Sore throat.

3. Painful lymph nodes in the anterior or posterior cervical or axillary distribution.

4. Unexplained generalized muscle weakness.

5. Muscle discomfort or myalgia.

6. Prolonged (24 hours or greater) generalized fatigue after levels of exercise that would have been easily tolerated in the patient's pre-morbid state.

7. Generalized headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the pre-morbid state).

8. Migratory arthralgia without joint swelling or redness.

9. Neuropsychologic complaints (1 or more of the following: photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty in thinking, inability to concentrate, depression).

10. Sleep disturbance (hypersomnia or insomnia).

11. Description of the main symptom complex as initially developing over a few hours to a few days (this is not a true symptom, but may be considered as equivalent to the above symptoms in meeting the requirements of the case definition).

Physical Criteria

Physical criteria must be documented by a physician on at least 2 occasions, at least 1 month apart.

1. Low-grade fever – oral temperature between 37.6 °C and 38.6 °C, or rectal temperature between 37.8 °C and 38.8 °C. (See note 1 under Symptom Criteria.)

2. Nonexudative pharyngitis.

3. Palpable or tender anterior or posterior cervical or axillary lymph nodes. (Note: lymph nodes greater than 2 cm in diameter suggest other causes. Further evaluation is warranted.)

* From Holmes GP, et al[12].

In contrast to most patients with chronic fatigue, 85% of patients with CFS experience the *sudden onset* of an illness that then becomes chronic. Typically, the patients with CFS state that their chronic illness began on a particular day, with an acute "infectious" illness characterized by fever, pharyngitis, adenopathy, myalgias, and related symptoms. Unlike the usual such acute illness, the patients state that they have never fully recovered.

Along with the fatigue, patients typically complain of other *chronic* symptoms, as summarized in Table 2. In our experience, 2 particularly remarkable findings are chronic post-exertional malaise and recurrent, often drenching night sweats. The post-exertional malaise is characterized not only by symptoms that could represent deconditioning – pain and weakness of the involved muscles – but also by exacerbation of "systemic" symptoms, e.g., fever and adenopathy.

The patients state that these symptoms and others were typically *not* a chronic problem in the years before the onset of their illness, but became common after the illness began. As an example, here is the frequency of several common chronic symptoms *after* the illness began vs. *before* the illness began: arthralgias (76% vs. 6%); morning stiffness (62% vs. 3%); distractibility (82% vs. 4%); forgetfulness (71% vs. 2%); dizziness (61% vs. 4%); paresthesias (52% vs. 2%); sleep disorder (90% vs. 7%); irritability (68% vs. 4%); depression (66% vs. 7%).

Of the patients we have been following, a few have had transient acute neurologic events: primary seizures (7%), acute profound ataxia (6%), focal weakness (5%), transient blindness (4%), and unilateral paresthesias (not in a dermatomal distribution). The clinical and laboratory findings in these relatively few patients with dramatic neurologic events are very similar to those of the larger group of patients with chronic fatigue, except for the neurologic events themselves.

On past medical history, the only clearly striking finding is a high frequency of atopic or allergic illness (in approximately 50%), as was first highlighted by Jones and his colleagues[17,18], and confirmed by Straus[19].

On physical examination (Table 2), unusual and abnormal findings are observed in 15-50% of our patients: fevers; unusually low basal body temperature (below 97 °F); posterior cervical adenopathy; and abnormal tests of balance (Romberg and tandem gait).

On standard hematologic testing, it appears that results outside the normal range are seen in 15-50% of patients: leucocytosis; leukopenia; relative lymphocytosis; atypical lymphocytosis; monocytosis; elevated sedimentation rates; and unusually low sedimentation rates. These results have not yet been formally compared to results in a control group of healthy patients.

Standard serum chemistry testing is remarkable only for modestly elevated transaminases on one or more occasions in a quarter of the patients we have seen. None of these patients has had serologic evidence of active infection with hepatitis A, B, or C virus.

On immunologic testing, we and others[14-16,18,20-22] have found evidence of subtle and diffuse dysfunction: partial hypogammaglobulinemia (25-80%); partial hypergammaglobulinemia (10-20%); low levels of autoantibodies, particularly antinuclear antibodies (15-35%); low levels of circulating immune complexes (30-50%); elevated ratios of helper/suppressor T-cells (20-35%); reduced EBV-specific cytotoxic T-cell activity; reduced *in vitro* synthesis of interleukin-2 and interferon by cultured lymphocytes; increased IgE-positive T and B cells; deficient functional activity of natural killer cells; anergy or hypoergy by skin testing; and elevated levels of various cytokines. Some investigators have found increased levels of circulating interferon, whereas others have not. Straus demonstrated a significant increase in levels of leucocyte 2',5'-oligoadenylate synthetase activity, an enzyme induced during acute viral infections[16]. In approximately half of the few patients who have had lumbar punctures there has been pleocytosis, predominantly lymphocytic, without other abnormalities.

Formal neuropsychologic tests of cognition performed by Bastien, Albert, and their colleagues (unpublished data) suggest that one-third to one-half of our patients have cognitive impairment – particularly impairment of concentration and attention. It is the judgment of the neuropsychologists that the pattern of test performance suggests an "organic" deficit, rather than cognitive dysfunction secondary to a mood disorder.

Table 2.
Frequency of Chronic Symptoms and Signs*

Symptom/Sign	Frequency
Fatigue	75-100%
Low-grade fever	60-95%
Myalgias	30-95%
Depression	70-85%
Headaches	35-85%
Pharyngitis	50-70%
Impaired cognition	50-70%
Sleep disorder	15-70%
Anxiety	50-70%
Adenopathy	40-60%
Nausea	50-60%
Arthralgias	40-60%
Diarrhea	30-40%
Cough	30-40%
Odd skin sensations	30-40%
Rash	30-40%
Weight loss	20-30%
Weight gain	50-70%
Low basal body temperature (95.0-97.6°F)	10-20%

*Adapted from the experience of the author, plus others[14-16]

Because of the cognitive and neurologic complaints, and because of the similarity of some of these symptoms to symptoms experienced by patients with multiple sclerosis, we obtained magnetic resonance images (MRI) of the brain. In the majority of over 100 patients studied in collaboration with our colleagues P. Cheney, R. Biddle, D. Peterson, and F. Jolesz, there were multiple areas of high-intensity signal in the subcortical white matter (unpublished data). A comparison with MRI findings in healthy control subjects of the same age and sex is being conducted.

Viruses and Chronic Fatigue Syndrome

As each of the chronic fatigue syndromes we have discussed has found its way into the medical literature, it has brought with it the speculation that the illness was initiated by an infectious agent. The speculation has centred most often on viruses, although Salit has suggested that non-viral infectious agents also can trigger a similar post-infectious malaise[23].

Myalgic encephalomyelitis was thought for some time to be produced by a less virulent strain of poliovirus. Recently Mowbray has kept alive the possibility that enteroviral infection may indeed be associated with some cases of CFS, by demonstrating the greater frequency of circulating enteroviral antigen in patients than in control subjects[24].

Epstein-Barr virus has also been the subject of investigation. Most studies of CFS patients have found higher levels of VCA-IgG and EA-Ab in patients than in matched, healthy control subjects; also, antibody to EBNA is absent in 10-30% of patients, whereas this is thought to be quite unusual in seropositive healthy individuals[14-16,25]. Moreover, it has been shown that antibody to EBNA-1 is absent in 10-30% of patients, and is absent more often in the more severely ill patients. Absence of antibody to EBNA-1 is very rarely seen in patients convalescing from acute infectious mononucleosis, or in patients with cancer. It is, however, seen frequently in children with acquired immunodeficiency virus (AIDS)[26].

There is no strong evidence that EBV plays a *primary* role in the pathogenesis of most cases of CFS: there are substantial numbers of patients who have normal (or absent) antibody levels to EBV but who are clinically indistinguishable from the other patients. Furthermore, there is clinical and laboratory evidence that other herpesviruses also can be reactivated in this illness; antibody to measles virus also may be higher[27]. Therefore, it seems most likely that the EBV serologic results in most patients with CFS represent *secondary* evidence of some immunologic perturbation, rather than a primary pathogenetic role for EBV. Nevertheless, secondary reactivation of EBV may not be just an epiphenomenon, as will be discussed shortly.

The recently discovered human herpesvirus 6 (HHV6) is an interesting candidate for a pathogenetic role in some cases of CFS, primarily because it is lymphotropic and gliotropic[28-30]. There appears to be a serologic association of this virus with both CFS and fibromyalgia[31-33], although some studies have not found such an association. Studies to assess active replication of HHV6 are now under way. At this time, the evidence seems most consistent with the hypothesis that this virus may be secondarily reactivated in this syndrome, as are other viruses; however, a primary role for HHV6 in the pathogenesis of this illness remains possible.

In this decade of the human retroviruses, it was inevitable that there should be some speculation linking retroviruses to CFS. We and others have found no evidence that any of the known human retroviruses are involved with this syndrome. Furthermore, we have found no evidence of reverse transcriptase activity in the supernatants of primary lymphocyte cultures from a number of our sickest patients.

Chronic Fatigue Syndrome and Psychologic Illness

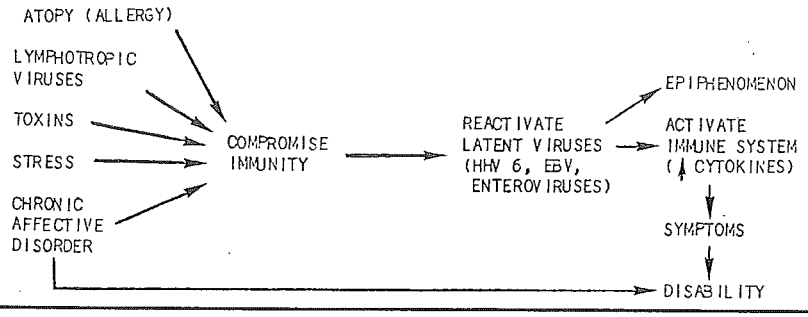
As stated at the outset, most patients seeking medical care for chronic fatigue probably are suffering from a primary affective disorder (depression and/or anxiety). Moreover, most patients seeking medical care for chronic fatigue probably do not have CFS[34,35].

What is the role, if any, of affective disorders in CFS? This is a difficult issue to study, since the affective disorders are defined in part by symptoms that could also reflect a "physical" illness. In our experience, most patients with CFS perceive themselves as becoming *secondarily* depressed and/or anxious following the (usually sudden) onset of their illness. According to data from a self-administered questionnaire, 80-90% of these same patients deny suffering from depression or anxiety in the years prior to their illness. Yet more intensive interviewing by a trained interviewer, using the Diagnostic Interview Schedule (DIS), suggests that affective illness predated the onset of CFS in a somewhat greater number of patients (unpublished data). Although it has been cited as evidence supporting the proposition that CFS is entirely a psychiatric disorder, the report by Kruesi and colleagues, using the same structured interview, found a rate of major depressive disorder of 7% in the period *prior to* the onset of CFS[36], a rate similar to that found in the population at large[37]. And the same team, studying largely the same patients, found abnormalities of the hypothalamic-pituitary-adrenal axis that were entirely different from those seen in patients with major affective disorder[38].

Even if it were true that patients with CFS more frequently have an affective disorder that predates the onset of chronic fatigue, what might that mean? Those who accept the classic Descartian notion of mind-body duality, who conceive of affective disorders as purely mental phenomena disconnected from the body, may conclude that the symptoms in patients with CFS reflect no physical abnormality, just a heightened awareness of and concern about physical sensations, possibly coupled with a desire to attribute their dysfunctional state to a physical illness.

I am more inclined to view affective disorders as biologically determined disorders of neurochemistry, disorders that can affect immune function and that, in turn, can be perturbed by external phenomena that perturb the immune system. According to this model, "mind" and "body" are not separate and discrete, but inevitably linked. It is, therefore, plausible that the biologic forces that increase the likelihood of affective disorder also may increase vulnerability to disorders of immunity. In patients with CFS, who have a current and/or past affective disorder and who

Figure 1
Current Favorite Model



also have evidence of immune dysfunction and active viral infection, it may never be possible to determine whether the affective disorder, the immune dysfunction, or the viral infection came first. Rather, the practical question is what form of therapy will be most effective: psychotherapy, pharmacotherapy of the affective disorder, "immune modulating" pharmacotherapy, anti-microbial therapy, or some combination of these.

Model for the Pathogenesis of Chronic Fatigue Syndrome

Knowledge about CFS is limited. The available data permit many models, but provide strong support for none of them. My own current view of this illness is reflected in Figure 1. At the core of CFS, I suspect, is an immunologic disturbance that allows reactivation of latent and ineradicable infectious agents, particularly viruses. The reactivation of these viruses may only be an epiphenomenon. However, I feel it is more likely that, once secondarily reactivated, these viruses contribute to the morbidity of CFS – directly, by damaging certain tissues (e.g., the pharyngeal mucosa), and indirectly, by eliciting an ongoing immunologic response. In particular, the elaboration of various cytokines (e.g., interferon-alpha and interleukin-2) as part of this ongoing immunologic war may produce many of the symptoms of CFS – the fatigue, myalgias, fevers, adenopathy, and even the disorders of mood and cognition. This is suggested by the finding of increased levels of various cytokines in CFS and related conditions[39-41], and the experience with infusing cytokines, made by recombinant DNA techniques, for various therapeutic purposes[42-48].

Whatever the course, the symptoms of CFS lead to some degree of debility in every patient. As with any illness, the degree of debility must be due, in part, to psychologic factors.

What triggers the immune dysfunction in the first place? It is likely that many factors could do so: an atopic diathesis, exogenous lymphotropic infectious agents, environmental toxins, stress and, as argued earlier, the biology of an underlying affective disorder. It seems unlikely that there is a single explanation, such as one infectious agent, for this complex illness.

Acknowledgement

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8. *Dual Infections of the Immune System in Patients with Chronic Active Epstein-Barr Virus Infection Mimicking Chronic Fatigue Syndrome*

D.T. Purtilo

Introduction

Several groups of investigators[1-4] have described a syndrome (chronic fatigue syndrome [CFS]) in which chronic debilitating fatigue associated with low-grade fever, painful or tender lymph nodes, myalgias, arthralgias, sore throat, headaches, neurologic complaints, and a variety of other symptoms are observed. Additionally, it often affects young women who are career-oriented [5-6]. Controversy about the etiology of CFS prevails for a variety of reasons. The major complaint – fatigue – is the seventh most commonly noted presenting symptom among patients receiving primary care[7]. Thus, physicians are challenged to differentiate CFS from a myriad of other disorders.

Although the etiologic basis of CFS is unknown at this time, substantial evidence points to the possibility that some of the patients suffer from a post-viral disease which lingers and is manifested chiefly by chronic fatigue. In this paper a variety of viruses is discussed which can infect and persist in the cells of the immune system. Also, the interaction between Epstein-Barr virus (EBV) and adenovirus type-2 (AD-2) is described as being possibly responsible for the existence of a subgroup of patients with chronic active EBV infection. These patients should be excluded from a diagnosis of CFS as they have identifiable etiologic bases for their disease, which mimics CFS.

Viruses Infecting the Immune System

Many viruses can replicate in the cells of the immune system (Table 1) and may disable immune-specific responses[8,9]. Teleologically speaking, a good strategy has occurred for viruses to infect the immune system, to elude immune responses, as well as for becoming passengers carried in the blood stream to various organs within these cells. Oldstone[8] notes that a common mechanism by which viruses initiate persistence is infection of immune cells ordinarily required to clear the virus itself (Table 2). The result is a selective advantage for the virus which causes immune suppression against itself. Whether CFS can arise from persisting dual viral infection of the immune system remains to be investigated.

Dual Viral Infection of the Immune System

The emergence of acquired immunodeficiency syndrome (AIDS) has prompted intensive investigation of the interaction of viruses with the immune system. In patients infected with the human immunodeficiency virus (HIV), we and others[10] have found that an extremely high prevalence rate of antibody to cytomegalovirus (range 92 to 100%), herpes simplex virus (range 90 to 100%), hepatitis B virus (range 78 to 82%), hepatitis A virus (range 82 to 95%), and EB viral capsid antigen (nearly 100%) prevails in such patients. Studies performed in our laboratory during 1983-84, revealed that 396 consecutive homosexual men from Greenwich Village were seropositive for EBV[11]. Generally, about 90 to 95% would be expected to be seropositive in the general adult population. Montagnier and colleagues initially employed EBV-transformed B cell lines *in vitro* to grow HIV concurrently[12].

Coinfection of B lymphocytes by EBV and HIV results in enhanced production of viruses[13]. Similarly, there is an enhanced EBV gene expression by other herpesviruses[14] in *in vitro* studies. Human herpesvirus 6 (HHV6) was initially isolated during attempts to identify retrovirus multiplying culture primary lymphocytes from patients with AIDS. Agut et al.[15] have noted that HIV-1 and HHV6 can simultaneously replicate and destroy lymphocytes in cultures from AIDS patients, thus confirming the report by Lusso et al.[16] that productive dual infection of human CD4+ T lymphocytes by HIV-1 and HHV6 can occur.

Chronic Epstein-Barr Virus (CEBV) Disease

Asymptomatic infection with EBV occurs in nearly all infants and children, whereas approximately two-thirds of young adults develop acute infectious mononucleosis (IM) after primary infection [17]. For more than 2 decades EBV has been known to be the cause of IM. Suggestions that CFS may arise from IM have implicated EBV as a possible etiologic agent. A well-documented acute EBV infection (demonstrated by IgM antibody to viral capsid antigen) or seroconversion to EBV and/or Monospot with atypical lymphocytosis is required. Subsequently, in a subset of patients the disease persists and antibodies to early antigen are also elevated for 6 months or longer, consistent with chronic infection with this virus. Some of these patients manifest lowered serum immunoglobulin and lowered anti-EBV determined nuclear antigen (EBNA titres suggesting the presence of B and T cell defects)[2]. Differential diagnosis of CEBV from CFS and other diseases is shown in Table 3. The EBV antibodies in CEBV are elevated; antibody titres to cytomegalovirus, herpes simplex virus types I and II, and measles virus have also been elevated, as described by Holmes et al.[18]. Hindering diagnosis was the failure of the various laboratories to show agreement regarding their EBV titres. A discrete group of patients with objective physical findings and laboratory aberrations have been described as having chronic active Epstein-Barr virus (CAEBV) disease.

Chronic Active Epstein-Barr Virus (CAEBV) Infection

Another syndrome to be considered in the differential diagnosis is chronic active EBV (CAEBV) which occurs in children and young adults who characteristically demonstrate fever, fatigue, lymphadenopathy, hepatosplenomegaly, pancytopenia, polyclonal gammopathy, and very high antibody titres to EBV (Table 3)[19]. In

Table 1.
Viruses that Infect Human Lymphocytes and Monocytes

Viruses[a]	Infected Cells[b]
Double-Stranded DNA Viruses	
Hepatitis B Virus	PBMC T and B lymph
Papovavirus	PBMC
Group C adenoviruses	T, B, and null lymph
Herpes simplex virus	T lymph
Eptsein-Barr virus	B lymph
Cytomegalovirus	lymph, mono
Positive-Strand RNA Viruses	
Poliovirus	lymph, mono
Rubella	T and B lymph
Negative-Strand RNA Viruses	
Measles	T and B lymph, mono
Mumps	T and B lymph
Respiratory syncytial virus lymph, mono	
Vesicular stomatitis virus	T lymph
Influenza A	lymph, mono
Parainfluenza	lymph, mono
Retroviruses	
HTLV I, III	T, B, and null lymph
HIV-1, 2	T and B lymph, mono

[a] Viruses that infect monocytes but not lymphocytes are not listed.
[b] Abbreviations: PBMC, peripheral blood mononuclear cell; lymph, lymphocyte, mono, monocyte or macrophage.

Adapted from: Oldstone, MBA. *Viral persistence.* Cell 1989; 56:517-20.

Table 2.
Mechanisms of Viral Persistence

Avoid Immunologic Surveillance

1. Remove recognition molecules on infected cells
   Alter viral protein expression
   Anti-viral antibody-induced capping and modulation
   Direct virus effect
   Indirect virus infection – release of lymphokines and monokines
   Absent in neurons
2. Abrogate lymphocyte/macrophage function
   Generalized immunosupression
   Lymphokines and monokines alter transcription of host gene(s)

Alter Replication and Transcription of Virus

1. Incompete or defective viruses
2. Generate mutants or variants
3. Diminish expression of viral gene product(s)

(From: Oldstone, MBA. *Viral persistence.* Cell 1989; 56:517-20. Copyright © 1989 by Cell Press. With permission of Cell Press.)

rare patients, concurrent infection with adenovirus type-2 and EBV has been demonstrated. These patients show extremely high EBV titres and the foregoing physical and laboratory findings[20].

Summary and Conclusion

The etiologic bases of CFS are undetermined at the present time. It is very important to distinguish the patients with CFS as defined by the Centers for Disease Control (CDC) case definition of Holmes et al.[21] from patients with physical and laboratory findings suggesting dual infections and/or underlying immunodeficiency. Particularly fruitful might be a longitudinal immunovirologic study of patients who exhibit CFS following a well-documented viral infection.

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Table 3.
Differential Diagnosis of Chronic Fatigue Syndrome and Related Disorders

	Chronic Epstein-Barr Virus Disease (CEBV)[1]	Chronic Active Epstein-Barr Infection Syndrome (CAEBV)	Immunodeficiency		Other Similar Syndromes	Chronic Fatigue Syndrome (CFS)
			Primary	Secondary[2] or AIDS		
Major Clinical Manifestations	Fever, lymph-adenopathy, fatigue (onset begins with acute infectious mononucleosis)	Fever, lymph-adenopathy hepatosplenomegaly (severe) and pancytopenia	Variable depending on type (i.e., XLP, AT, WAS, CVI)	Secondary to the disease	Severe muscle fatiguibility psychiatric manifestations	Often debilitating fatigue, fever
Gender	More females	No differences	More males	Males dominant in AIDS	More females	More females
Age Distribution	Mostly adults	Mostly children (<15 years)	Mostly children	Mostly adults	Mostly adults	Mostly adults
Clinical Course	Uncertain	Often lethal	Often lethal	Often	Uncertain	Uncertain
Antibody Titres to Epstein-Barr Virus	Reactivation with moderately high antibody titres to IgG-VCA[5] and IgG-EA[6] with low antibody titres to EBNA	Extremely high antibody titres of IgG-VCA and EA and positive IgG-VCA[8]	Reactivation with low antibody titres to EBNA	Reactivation pattern. Generally normal antibody titres to EBNA	Unknown	Normal seropositive or seronegative

(From: Thiele GM, Okano M, Purtilo DT. *Differential diagnosis of chronic fatigue syndrome: an update. Infections in Medicine.*)

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9. *Human Herpesvirus 6 (HHV6) and Chronic Fatigue Syndrome (CFS)*

D.V. Ablashi, C. Zompetta, C. Lease, S.F. Josephs, N. Balachandra, A.L. Komaroff, G.R.F. Krueger, B. Henry, J. Lukau and S.Z. Salahuddin

Human herpesvirus 6 (HHV6) (Figure 1) was originally isolated from the peripheral blood mononuclear cells from patients with lymphoproliferative disorders, acquired immunodeficiency syndrome (AIDS), and other malignancies[1]. The virus was characterized as distinct from the other members of the human herpesvirus family by the employment of immunologic and molecular analyses[1,2]. The cell tropism of HHV6 infection suggested a wider host range than was originally thought[3,4]. Further sero-epidemiologic investigation of the prevalence of HHV6 was based on the development of other immunologic assays[5,6]. Since its isolation in 1986, a considerable number of new HHV6 isolates have been reported from healthy individuals, AIDS, chronic fatigue syndrome (CFS), and transplant patients, as well as from patients suffering from other diseases (Table 1)[5,7,8]. Genomic analysis of HHV6, GS strain (the first reported isolate)[1,2], is described in Table 2. Further molecular analyses revealed that HHV6 isolates show divergence[9]; an example of such a finding is shown in Figure 2. In the early studies of CFS patients Epstein-Barr virus (EBV) was considered to be implicated in CFS, based on the detection of elevated antibody titres to EBV VCA and EA IgG[10-12]. In fact, based on these studies, CFS was called "Chronic EBV Syndrome." Epstein-Barr virus strain differences are commonly observed in AIDS patients and in patients with other malignancies. Thus, it is biologically and immunologically important to know whether EBV isolates from CFS patients are different. Later studies on large groups of patients failed to establish a strong link between CFS and EBV. The clinical manifestations of CFS described by Komaroff and others[10,11,13,14] strongly suggested a viral etiology. It is surprising that, while EBV was implicated as a possible etiologic factor in CFS, no isolation of EBV from a CFS patient has been described in the literature; such isolation is required to determine any strain differences that would be useful for further sero-epidemiologic and other immuno-virologic analysis.

We began looking for an association between HHV6 and CFS in 1987. Evidence of a 78% prevalence of HHV6 antibody and elevated titre (>1:160) to HHV6 (GS strain) was first detected by indirect immunofluorescence assay (IFA) (Figure 3) in sera obtained from Lake Tahoe, Nevada, Boston, Massachusetts, and the National Institutes of Health (NIH)[5]. In comparison, there was a prevalence rate of 58% and antibody titres ranging between 1:10 and 1:160 in normal donors, with a majority having a titre of 1:40. In a later study of approximately 300 CFS patients possessing the clinical criteria described in Table 3, 51% had HHV6 VCA/IgG >1:160 with considerable numbers of patients having titres of >1:320 ≥1:5120. About 25% of the sera also showed elevated antibodies to EBV VCA. Surprisingly, about 20% of the sera also contained elevated VCA/IgG antibodies to both HHV6 and

Figure 1
Electron Micrograph of Extracellular HHV6 (GS strain) Particles from Cultured Mononucleated Cell. The Insert shows a Detailed Structure of a Single Virion.

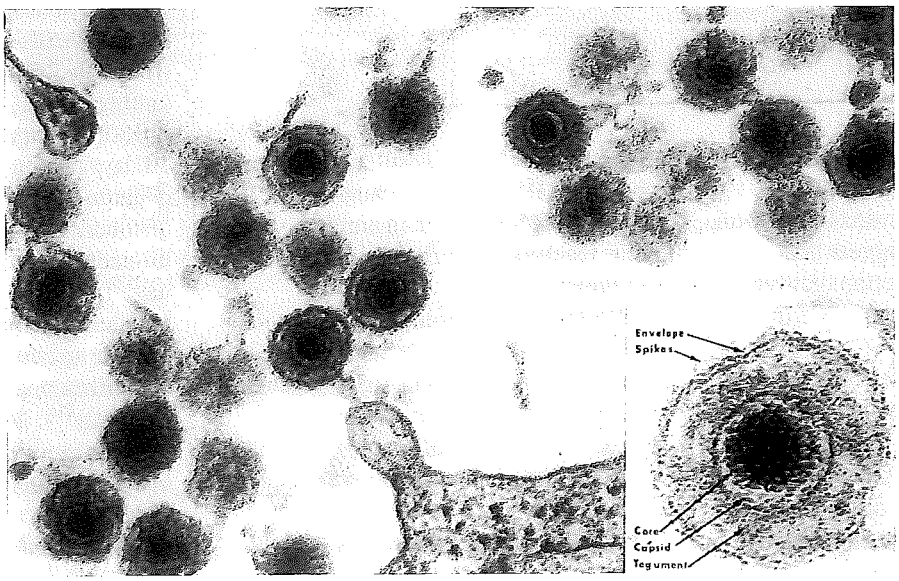


Table 1.
Reports of HHV6 Isolations to Date

Investigator	Source/Patient	Reference
Salahuddin et al.	AIDS, other lymphoproliferative and malignant diseases	Science, 1986
Downing et al.	HIV+	Lancet, 1987
Tedder et al.	HIV+	Lancet, 1987
Becker et al.	Hairy Cell Leukemia/HIV+	Int Virol Cong, 1987
Feorino et al.	HIV+	Int Virol Cong, 1987
Lopez et al.	HIV+	J Infect Dis, 1988
Yamanishi et al.	Infants with roseola	Lancet, 1988
Kikuta et al.	Children with exanthum subitum	J Infect Dis, 1989
Ablashi et al.	Chronic Fatigue Syndrome, HIV-1, AIDS	J Virol Methods, 1988; 1989 (unpublished)
Kaplan et al.	AIDS	Lancet, 1988
Agut et al.	HIV-1, -2, AIDS	Res Virol, 1988
Pietroboni et al.	Normal donors' saliva	Lancet, 1988
Carrigan et al.	Chronic lymphopenia, Legionaires disease	Am J Med, 1989
Ward et al.	Liver transplant	J Med Virol, 1989
Krueger et al.	SLE, ECVD	Am J Med, 1989

Table 2.
Human Herpesvirus 6 Genome

- Double-stranded DNA genome
- Size is 155,000 to 170,000 base pairs
- 40-44% GC
- Coding capacity > 70 proteins
- Genomic inversion inapparent
- Integration? (unknown)
- Closest phylogenetic relative: HCMV
- Contains repetitive sequences
- Restriction site polymorphism among different isolates
- Polymorphic variants occur upon passage
- Thymidine kinase deficient

EBV. In the healthy controls selected from the same areas, HHV6 and EBV antibodies were only elevated in 6-8% of the sera. This finding suggests that perhaps there is an interaction between HHV6 and EBV, which may contribute to disease manifestation.

Further analysis of the serum samples from a few CFS patients showed that, even though EBV VCA titres may have been elevated, they were stable over a short period of time. But a rise and fall in HHV6 antibody further supports the theory of frequent reactivation of HHV6 (Figures 4 and 5). It is still not clear how and when HHV6 is reactivated and whether this fluctuation in antibody and virus reactivation correlates with CFS symptoms.

It is known that primary infection of HHV6 leads to exanthem subitum (roseola) in infants[8] and virus-infected cells were CD4 positive. A similar disease without the rash may be observed in older children after primary infection (Figure 6). Moreover, 12% of the heterophile-negative infectious mononucleosis cases are the result of primary HHV6 infection[15,16], where HHV6 IgM antibody is detected without the presence of IgG in the acute stage of the disease. A self-limiting febrile illness has also been observed in renal and liver allograft patients as a result of HHV6 infection[7,17]. About 70% of AIDS patients possess HHV6, although there may be local differences in antibody prevalence according to risk group of human immunodeficiency virus (HIV) positive and to hygienic conditions. The *in vitro* double infection of CD4 cells by HIV-1 and HHV6 led to enhanced killing of cells and an increase in HIV[18]. It is probable that in AIDS HHV6 reactivation may be contributing to enhanced immunosuppression and indirectly to clinical manifestations[18-20]. Patients with collagen vascular diseases show an HHV6 antibody prevalence of 90% as compared to 60% in healthy controls. The risk of HHV6 reactivation is about 50% in systemic lupus erythematosus (SLE) and in Sjogren's syndrome (SS), based on IgM titres of above 1:40 and/or IgG titres of above 1:640.

We began to examine the cells from CFS patients by IFA for expression of viral antigens, employing monoclonal antibodies to HHV6 proteins and glycoproteins[21] in an attempt to isolate the virus and to see how frequently the HHV6 antigen-expressing cells were observed in patients with acute illness. Most of the patients in this study were from Lake Tahoe, Boston, and New York. Of the 28 patients studied thus far, 64.3% expressed HHV6 antigens when their cells were grown in culture with phytohemagglutinin (PHA). The range of cells expressing antigens was from 4 to 35%. The cells expressing antigens (P41, P116/64, P135, gp82, gp180/200) appeared at between 2 and 10 days and began to degenerate quickly (Figure 7). These cells were quite distinctive, i.e., large, refractile mono- or bi-nucleated, as previously observed by us[1,5]. The IFA reactivity with monoclonal antibodies varied from nuclear to cytoplasmic, depending upon the infection and the specificity of the antibody[21]. In comparison, only 1% or less of the normal donors' cells were reactive. Human herpesvirus 6 was isolated from a CFS patient from Boston. Her peripheral blood lymphocyte samples, which were taken 5 months

Figure 2
Molecular Comparison of two HHV6 Isolates.
The Arrows show Bands which are not Present in HHV6 Z-29 Isolate.

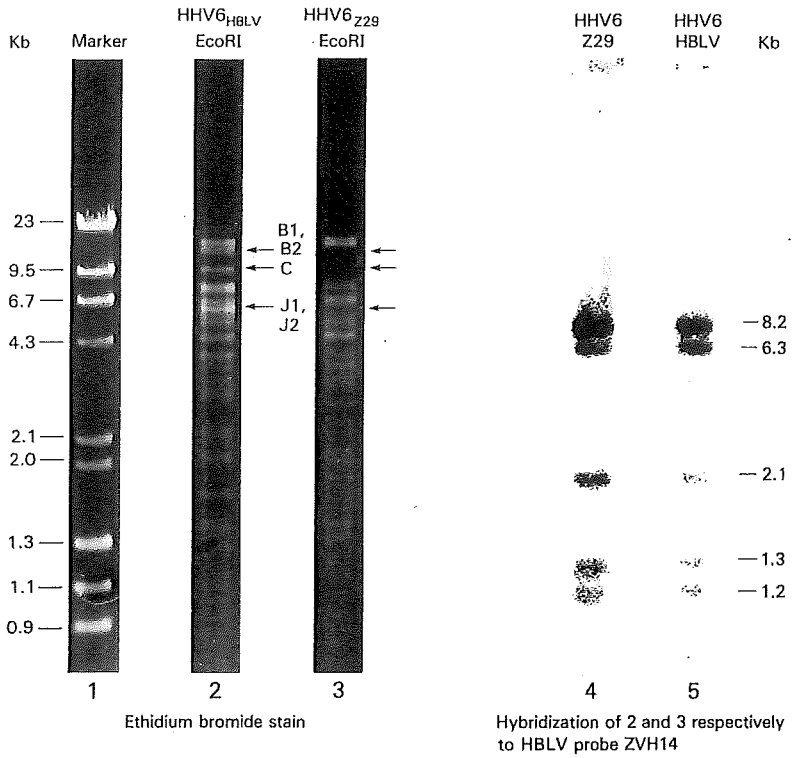


Table 3.
Clinical Criteria for Chronic Fatigue Syndrome (CFS) Used for Serological Investigations for HHV6 Antibody

- Syndrome lasting more than 6 months (prolonged > 6 months; chronic > 18 months)
- Mental changes (confusion, lack of concentration, anxiety, depression)
- Joint, muscle aches or myalgia during normal activity-proximally general muscle weakness
- Chills, low grade fever
- Recurrent headache
- Flushing of ears and neck
- Parasthesias
- Dizziness
- Sleep disorder

May or May Not be Present

- Palpitations, MVP
- History of acute illness
- Sore throat localized to specific area
- Appetite loss
- Non-exudative pharyngitis
- Diarrhea
- Weight loss
- Food and drug allergies

Patient Type

- Often intelligent, hardworking, generally "achievers"
- More females than males
- Ages between 20 and 40

Figure 3
Infection of Different Cell Types with HHV6 (GS strain).

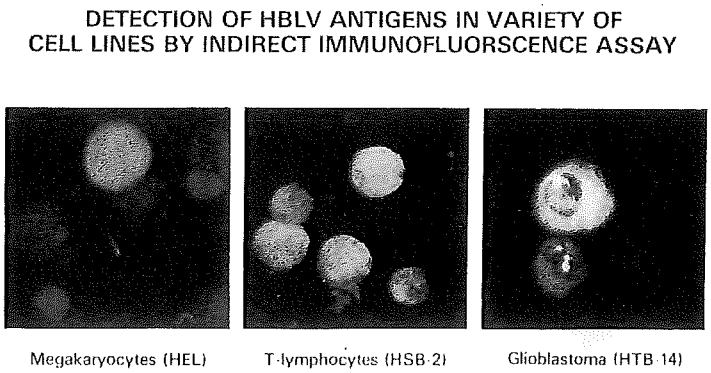
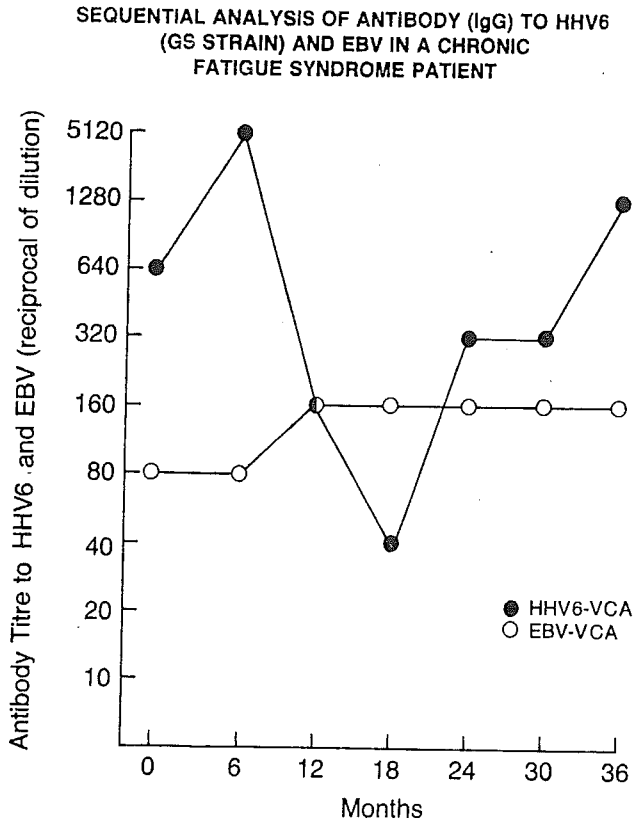


Figure 4
Comparison of HHV6 and EBV Antibody (IgG) from a CFS Patient.



apart, contained 10-30% HHV6 antigen-positive cells. The further characterization of this isolate is in progress (Komaroff et al., unpublished data). Thus, these data further suggest that this group of patients had active HHV6 infection. Using ZVH14 HHV6 probe, *in situ* data showed that at least twice the number of cells from CFS patients contained HHV6 genomes. Even though, in some patients, EBV genomes were detected, no active virus replication was evident in the cultured cells using EBV VCA and EA monoclonal antibodies.

The reactivation of HHV6 was further substantiated by the detection of HHV6 IgM antibody in 10 out of 24 patients (Table 4). No IgM antibody was detected in sera obtained from 12 normal donors by IFA following absorption with RF absorbent (Behring Werke, Marburg), or with protein G. Human herpesvirus 6 membrane antigen (gp180/200) was detected in 11 out of 25 acutely ill patients. The data presented in Table 4 show that during acute illness there is considerable activation of HHV6. Whether this activation is due to other viruses, steroids, hormones, or other immunologic activators is not known. Diffuse musculoskeletal pain of the axial skeleton is the most common feature in CFS patients[10,11,13,14,22]. Detection of EBV DNA in the muscle of 7 post-viral CFS patients was reported by Archard et al.[22]. The finding of EBV DNA in the muscle biopsies of CFS patients suggests that EBV may be implicated; however, the studies of Archard et al.[22] did not exclude the possibility of infiltrating lymphocytes in the muscle, which may account for the EBV DNA. Moreover, such biopsies were never tested for HHV6 DNA. Muscle biopsies seen by us showed signs of single-fibre degeneration without an inflammatory response. There was suggestive evidence for HHV6 genome in proliferated perimysial cells. *In vitro* skin fibroblasts can be infected with HHV6, and these cells express HHV6. Recently, HHV6 from fibroblasts of a CFS patient has been isolated, which raises strong possibilities that HHV6 may play an important role in myalgias in CFS.

The fact that HHV6 can infect monocytes/macrophages raises another possibility: that monocytes/macrophages

Figure 5
Elevated Antibody (IgG) to HHV6 and EBV to VCA in a CFS Patient.

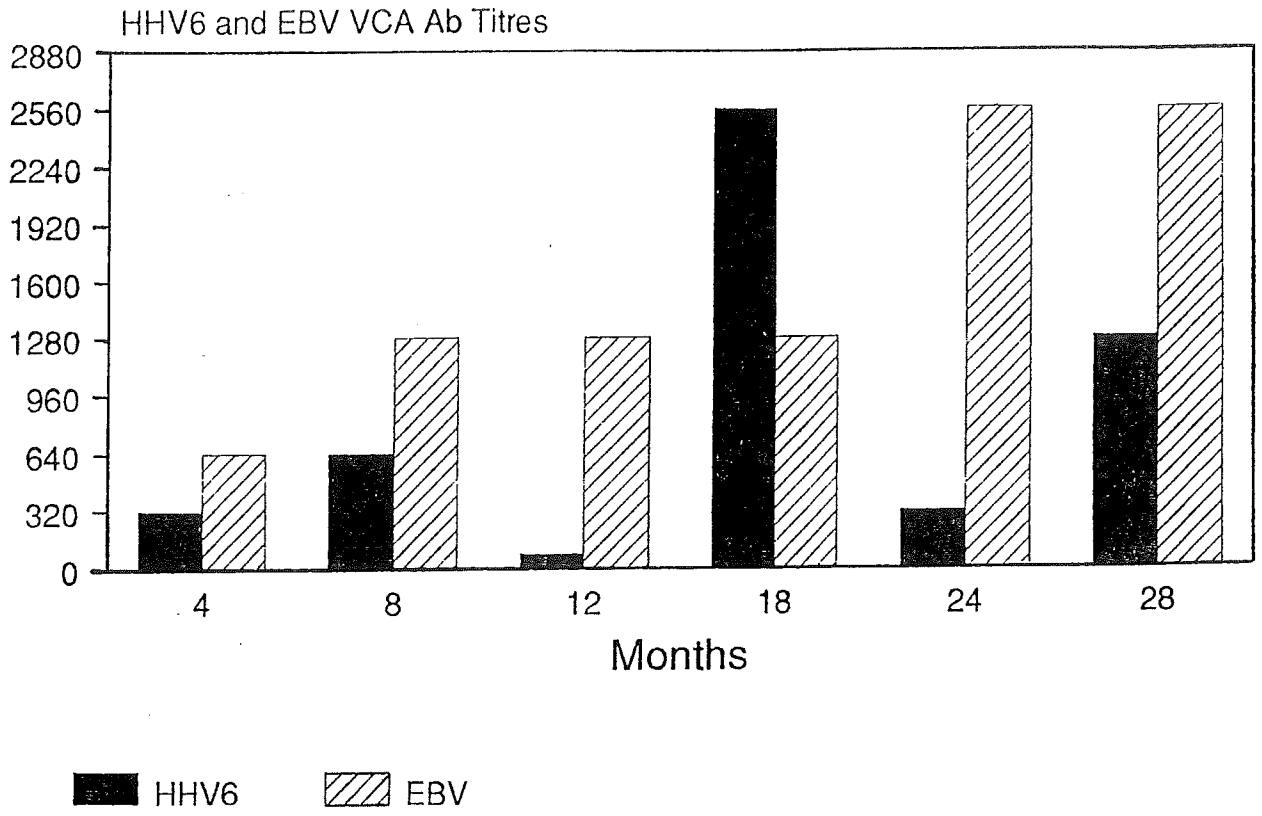
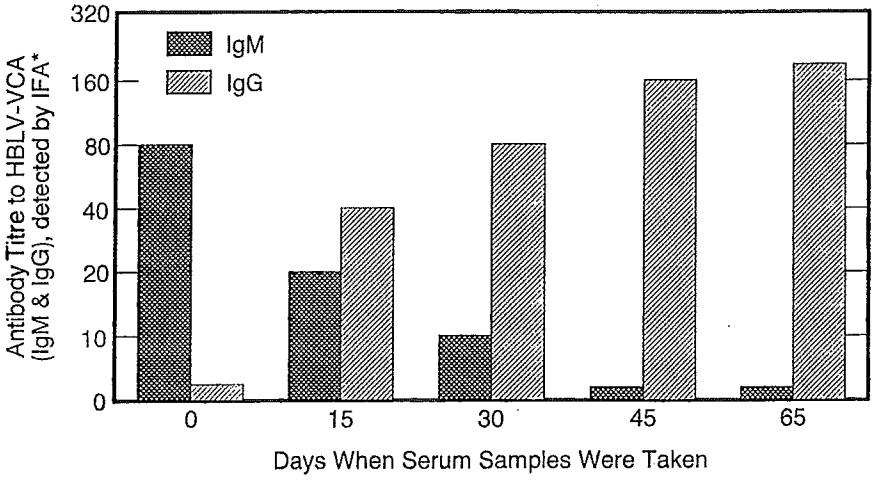


Figure 6
Evidence of Primary HHV6 Infection.



*Initial Serum Dilution for Testing Was 1:10

may infiltrate neurologic tissues where they may induce cytopathic effects. This finding is supported by the infection of glioblastoma cells with HHV6 (Figure 3)[3]. Thus, the infection of neural cells by HHV6 may contribute to neurologic disorders reported in some CFS patients. In-depth investigations are needed to analyze these tissues before conclusions may be drawn.

The questions yet to be answered are as follows:

(a) What causes CFS?

(b) What are the roles of HHV6 and EBV in the pathogenesis of CFS?

(c) Does the interaction of HHV6 and EBV lead to altered immune response?

(d) Is EBV and/or HHV6 latently present in CFS patients, activated by other non-viral agents which may contribute to disease manifestations?

If HHV6 were to be considered a major co-factor in CFS etiology, could the suppression of virus activation by

Figure 7
Cultured Lymphoblastoid Cells from a CFS Patient Showing Large Refractile Cells (phase contract) which were HHV6 Antigen Positive, using HHV6 Monoclonal Antibody.

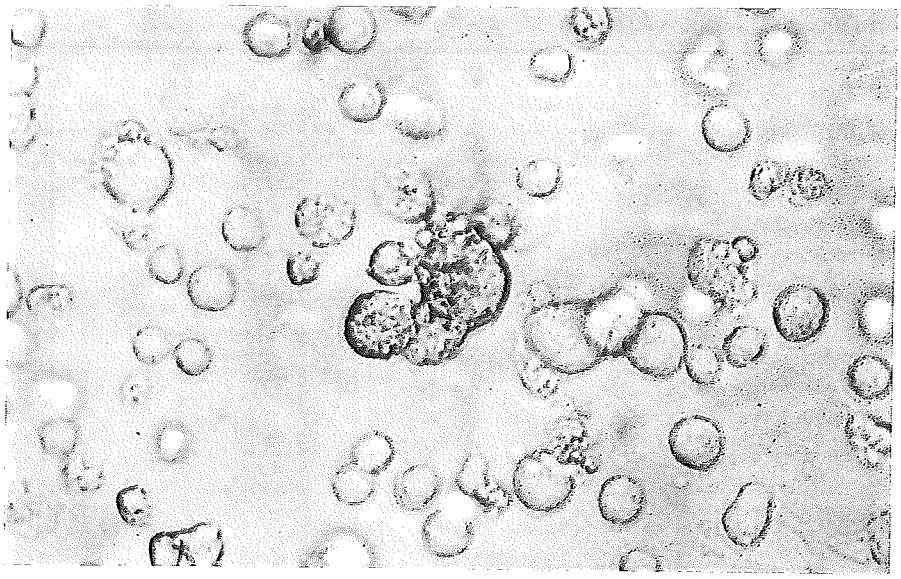


Table 4.
Reactivations of HHV6 in CFS Patients

Patients/ Normal Donors	No. Tested	No. Positive for IgG (Titre Range)	No. Positive for IgM (Titre range)	Detection of HHV6 Antigen in Peripheral Blood*
CFS	25	24 (80 - > 5120)	10 (10 - ≤ 80)	11/25
Normals	12	9 (20 - ≥ 80)	0	1/9

N.B. HHV6 (GS strain)-infected HSB2 cells were used in the IFA to detect IgG and IgM antibody.
* Monoclonal antibodies to HHV6 (GS strain) were used to detect HHV6 antigen expressing cells after cells were in culture for 3-12 days. The number of cells expressing viral antigen varied from 5-≥ 25% in CFS patients' lymphocytes and>2% in normal donors' lymphocytes.

Table 5.
***In Vitro* Effects of Antiviral Drugs on HHV6 Infection**

Treatment	Cell Number/mL	% IFA Positive Cells
HHV6 control (no drug)	$2x10^6$	≥ 72
Acyclovir (50 and 80 μg/mL)	$2x10^6$	< 65
Gancyclovir (50 and 80 μg/mL)	$2x10^6$	≤ 50
AZT (50 μg/mL)	$2x10^6$	≤ 68
Phosphoacetic acid (25 μg/mL)	$2x10^6$	< 0.5
Phosphonoformate (20 μg/mL)	$1.8x10^6$	0

* 80 μg/mL dose of Acyclovir or Gancyclovir was slightly toxic to HSB2 cells, in which the effects of these drugs were tested on HHV6 infection.

antiviral agents delay or prevent the onset of this disease[23-26]. Table 5 shows that phosphonoformate (PFA) and phosphoacetic acid (PAA) are effective in inhibiting HHV6 replication. A recent report by Russler[24] showed that Gancyclovir was able to block the infection of human mononuclear cells by their HHV6 isolate. Both of the compounds (Acyclovir and Gancyclovir) were highly effective against CMV, but did not inhibit the infection of cells of HHV6 GS isolate, as shown in Table 5. The difference could be due to GS isolates being more cytotoxic and highly replicative than theirs. This observation further suggests a need to screen various HHV6 isolates, particularly those from CFS patients with various antiviral compounds, for their effectiveness before further conclusions can be made. We feel that more awareness of CFS on the part of the physician, patient, and basic and clinical researcher in the coming years will greatly enhance our understanding of this illness, which is now being reported from other parts of the world[19,22,27]. Clinical trials and laboratory experiments are necessary in order to observe the antiviral effects of various compounds which may diminish the replication of HHV6 and EBV[23-26].

Acknowledgement

We thank Kristinë L. Ablashi for technical assistance in the preparation of this report.

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10. Summary — Session B

I.E. Salit

Summary

Dr. Anthony L. Komaroff from Brigham and Women's Hospital, Boston, was the initial speaker in this section. He reviewed the clinical features of chronic fatigue syndrome (CFS). He indicated that the demographics are not as restricted as were once thought to women between the ages of 20 and 40. Psychologic symptoms are common but may not be apparent on initial questioning. However, some symptoms clearly cannot be explained on a purely psychologic basis. He described a variety of neurologic complaints which generally had a frequency of 5-7%. An important physical finding was the presence of posterior cervical lymphadenopathy in 35-45% of patients and abnormal neurologic findings in about 30%. He reviewed some of the abnormal laboratory tests, which included the presence of immune complexes, elevated IgG or IgM, and increased IL2. Magnetic resonance imaging showed hyperintense signals in the white matter. Dr. Komaroff then reviewed possible candidate agents that may be the cause of CFS. There is no evidence for a retrovirus as the causative agent, nor is *Borrelia burgdorferi* (the agent of Lyme disease) a causative agent. Enteroviruses may be important since there is significantly increased activity in CFS patients versus controls. There is, however, also a higher antibody titre to the Epstein-Barr virus (EBV) as well as herpesviruses in this condition. The antibody titre to human herpesvirus 6 (HHV6) is higher in CFS patients than in controls. It does not appear to be the only causal agent and there has been no single causal agent identified. Dr. Komaroff then presented an hypothesis that incorporated some of the known factors in this illness.

Dr. David T. Purtilo, Omaha, Nebraska, reviewed mechanisms for viral persistence and emphasized that there are many latent viruses that infect lymphocytes and monocytes. There are instances when dual infections may be significant for the production of illness and he gave the example of the combined infection by human immunodeficiency virus (HIV) and EBV which can result in lymphoma or oral leukoplakia. He also gave a detailed example of a patient with severe disease. This patient had very high EBV antibody levels and both EBV and adenovirus type-2 were isolated. Another patient was noted to have HHV6. The varying titres correlated with changes in the immune complexes as well as with the patient's symptoms. He reviewed the differential diagnosis. There is a syndrome of chronic active EBV infection and EBV can reactivate in patients with various immunodeficiency syndromes including acquired immunodeficiency syndrome (AIDS). In CFS, the EBV titres are similar to those of the controls.

Dr. D. Ablashi from the National Cancer Institute, Bethesda, described HHV6 and its relationship to CFS. Human herpesvirus 6 has double-stranded DNA. It has a tegument similar to CMV. The GC content, however, is similar to varicella-zoster virus (VZV). It has the coding capacity for 70 polypeptides. So far no homology has been found with other herpesviruses but the genome has only partially been characterized. There is some polymorphism as noted by restriction site analysis. There are strains that are rapid-growing and cause death of cells whereas others are slow-growing with considerable cell, viability remaining. The serology for HHV6 is quite specific. The target cells primarily include CD7, CD2, and CD4 lymphocytes. About 60% of American blood donors have antibody and about 80% of children in the United States have antibody, implying that some antibody is lost through aging. In some parts of Africa almost 90% of people are infected and they have very high titres. Significantly, more CFS patients than controls have antibody to HHV6. There are large fluctuations in antibody titres to HHV6 in one individual over time and this does not occur with other herpesviruses. Human herpesvirus 6 also seems to reactivate in AIDS. Elevated antibody is also found in patients with thyroiditis. A muscle biopsy was shown which demonstrated HHV6 antigen in the muscle cells. Some antiviral agents show considerable activity against HHV6. These include Foscarnet (phosphonoformate), phosphoacetic acid, and Gancyclovir. Acyclovir, AZT, and Ara C do not have activity.

Session C
Laboratory and Other Diagnostic Evaluations

11. Search for an Association between Epstein-Barr Virus Infection and the Chronic Fatigue Syndrome

J.H. Joncas

The Epstein-Barr virus (EBV) infection is accompanied by a characteristic antibody response. Viral capsid antigen (VCA) antibodies appear first after infection and are already present in virtually all patients at the onset of infectious mononucleosis, a primary EBV infection. Viral capsid antigen immunoglobulin M (IgM) antibodies usually last for 2 months or less while VCA IgG antibodies persist usually for life. Early antigen (EA) antibodies appear at approximately the same time but in only 50-70% of patients. They disappear in most patients within a few months but may persist for several years at a titre of less than 1:100. EB nuclear antigen (EBNA) antibody response is delayed for periods varying from a few weeks to 5 or 6 months in most patients (90%)[1,2].

In contrast, in patients with chronic active EBV infection [3,4,5] either the EA antibody response is greater than 1:100 and sustained or the EBNA response is delayed indefinitely or is extremely weak. Both of these abnormalities may be seen in the same patient. In addition, several nonspecific immunologic abnormalities have been noted in these patients and occasionally in other members of their families not yet infected by EBV (Tables 1,2,3, and 4). The low (K-NK) cell cytotoxicity may be a primary defect in these patients since it is observed in both affected and unaffected patient's siblings (Tables 1 and 2). All the other abnormalities appear to be acquired following the EBV infection, abnormal EBV serology (Tables 1 and 2), inverted CD4 (T4/CD8 (T8) ratio (Table 3), and increased IgG-1 levels (Table 4). These patients have persistent splenomegaly, bouts of unexplained fever 2 and 3 times a year or recurrent attacks of pancytopenia responding to short courses of corticosteroids, but interestingly, they do not complain of fatigue. Nevertheless, in view of the fact that we had seen a rare patient with well-documented primary EBV infection going on to develop CFS, we decided to screen a large number of sera for EBV-EA and EBNA antibodies. These sera had been received by the National EBV Reference Service at the Ste-Justine Hospital over the past 4 years with the diagnosis of CFS or chronic mononucleosis. We used all the other sera sent to the same laboratory as controls except those from acute primary EBV infection. Except for sera from organ transplant donors or recipients,

Table 1.
Specific Epstein-Barr Virus (EBV) Serology, ADCC Antibodies, Leu 11 Positive Cells, NK and K Cell Function in Patients with Chronic Active EBV Infection in Three Families

Patients	EBV Antibodies VCA	EA	EBNA	ADCC Titre	K Cell Function	NK (After Interferon)	LEU 11% (No./mm^3)
A1	640	160 (D)	<5	<10	16.2 ± 4.5	25.5% (25.1)	3.0 (68)
A2	320	5 (D)	10	≥1000	19.7 ± 4.7	36.8% (55.8)	13.0 (121)
A3	20,480	2560	80	≥1000	3.6 ± 1.4	8.0% (8.7)	2.0 (38)
A4	<5	<5	<5	<10	5.7 ± 1.6	32.5% (49.2)	2.0 (42)
B1	80	10 (R)	320	≥1000	11.7 ± 3.0	32.9%	6.6 (213)
B2	40	40 (R)	40	100	8.7 ± 3.6	52.6%	22.0 (374)
B3	640	640 (R)	640	≥1000	6.0 ± 3.1	4.6%	6.0 (171)
B4	<10	<10	<10	<10	6.0 ± 1.3	34.0%	12.0 (547)
C1	1,280	5 (D)	20	≥1000	31.8 ± 2.5	84.6%	14.0 (350)
C2	320	5	320	10	17.5 ± 0.6	57.8%	15.0 (585)
C3 (monosomy 7)	2,560	320 (D)	20	≥1000	2.8 ± 0.1	6.8%	0.0 (0)
Co				>1000	18.1 ± 6.4	53.0% (69.2)	8.6 (244)

Legend: Families: A, B, and C
Co: Controls matched for age and sex
1 and 2: Father and mother
NK done on K562 cells
EBV-specific K cell function and ADCC titre done on EBV superinfected Raji cells; with test sera and normal reference effector cells for ADCC titre; or with a reference positive serum and patient cells as effector for K cell function. EBV antibodies by indirect or anticomplement immunofluorescence.

Table 2.
T4/T8% and Ratio Versus EBV Serology in Patients with Chronic Active EBV Infection

Patients and Other Family Members	Birth Date	Date of Sampling	EBV Antibodies MA	VCA	EA	EBNA	ADCC	T4/T8% (ratio)
Family A								
Affected	12/43	3/79		640	80	<5		
Father		1/82		640	160 (D)	<5		
		1/83						24/33 (0.7)
		3/86	<20				<10	
		5/86					<10	
		2/88	<20	640	40 (D)	<5		17/23 (0.7)
Asymptomatic	3/44	3/79		320	5	5		
Mother		1/82		320	5 (D)	10		56/12 (4.7)
		3/86		320	5 (D)	10	≥1000	
		5/86	>20<200					
		2/88	>20<200	320	5 (D)	10		28/6 (4.6)
Affected	7/74	8/78		0	0	0		
Daughter		9/78		640	20	20		
		5/80		640	80	40		
		1/82		2560	160	80		20/59 (0.3)
		1/83		>20,480	2560	80		24/55 (0.4)
		12/85					1000	
		3/86	>20<200				>1000	
		5/86		20,480	2560	20	1000	
		2/88	>20<200	10,240	1280	<10		19/53(0.36)
Seronegative	4/79	1/82		<5	<5	<5		51/20 (2.5)
Sibling		3/86	<20	<5	<5	<5	<10	
		9/87		<5	<5	<5		
Family B								
Affected	12/79	12/85		640	640 (R)	640		
Son		2/86						30/15 (2.0)
		3/86		640	640 (R)	640	>1000	
		9/86	>20<200				>1000	
		2/88	>20<200	320	1250 (R)	320		8/18(0.44)
Family C								
Affected Son	5/75	3/86	>20<200	2560	320 (D)	20	>1000	8/5 (1.6)
(monosomy 7)		5/86						2/4 (0.5)
		9/86		1280	320 (D)	20	1000	8/5 (1.6)
		10/87		320	80 (D)	20		
		2/88	20	320	80 (D)	10		4/3 (1.3)
Controls (for 3 families) 18-59 years								50±10/25±10(2±0.8)

Table 3.
NK* Cell Function in Patients with Chronic Active EBV Infection

Date	Family A				Family B				Family C			Controls (for 3 familes)	
	FA(A)	MO	DA(A)	SNS	FA	MO	SO(A)	SNS	FA	MO	SO(A) (mono-somy 7)	18-59yrs	7-12 yrs
3/79	10.0%												
1/82			0.2%										
9/82		25.2%(36.2)	9.0%(8.4)	34.9%(41.6)									
11/82			8.0%(8.7)										
1/83	25.5%(25.1)	36.8%(55.8)	5.1%(8.0)	32.5%(49.2)									
8/83	6,6.5,19.3**		9.5,7.8,7**									62.1±5.8%	50.8±11.0%
2/86						58.5%	9.2%	30.3%					
3/86					32.9%	52.6%	4.6%	34.0%	84.6%	57.8%	6.8%		
5/86	39.3%	36.9%	24.7%	21.9%									
9/87					33.9%	48.7%	9.1%						
1/88		54.1%	13.1%	32.8%									
2/88	37.6%	52.3%	13.7%		34.8%	52.8%	9.5%	21.9%			2.3%		

Legend FA(A): Affected Father; FA: Father; MO: Asymptomatic Mother; SO(A): Affected Son; DA(A): Affected Daughter; SNS: Seronegative Sibling
* NK cell function expressed as % of ^{51}Cr release from K562 cells. ( ): NK following interferon *in vitro*. Abnormal values.
** NK pre-, per, and post-intravenous Acyclovir therapy for 2 weeks

Table 4.
IgG Subclasses in Patients with Chronic Active EBV Infections and in Controls

	IgG-1 g/L	Mean	S.D.*	P**
Patient A1	16.040			
Patient A3	13.200	12.535	±2.336	
Patient B3	10.900			
Patient C3	10.000			
Control 1	5.700			<0.01
2	7.900			
3	5.700	7.140	±1.371	
4	9.300			
5	7.100			
Asymptomatic Family Members				
A2	6.400			
A4	5.000			
B1	8.400			
B2	4.100			
B4	8.400			
C1	6.200			
C2	5.700			

* Standard Deviation
** By two-tailed Student t test
A, B, C,: Family A, B, C
1: Father 2: Mother 3: Son or dauther with chronic active EBV infection
4: EBV seronegative sibling

these "control sera" came from patients with diseases resembling infectious mononucleosis or suspected of being of EBV etiology. We finally screened, for IgG-1 serum level, a subset of 27 sera from the same number of patients with CFS referred to the diagnostic virology laboratory at Ste-Justine Hospital. These patients had EBV-EA antibodies in titres ≥1:100. The methods used have been described previously[2,3,4].

The results are shown in Tables 5,6 and 7. Two hundred and seventy-eight sera were received with the diagnosis of CFS or chronic mononucleosis. Twenty of these sera were EBV negative for all EBV antigens, 167 had EBV-EA antibodies at a titre of less than 1:10, while 91 had EBV-EA titres of more than 1:10, and only 6 of these had a titre above 1:100. The prevalence of EBV-EA antibodies (≥1:10) in CFS versus controls was found to be 32.7% versus 18.4% (Table 5). This difference is tentatively interpreted as the result of EBV reactivation, which could be more frequent for as yet unknown reasons in CFS than in other individuals.

More interestingly, a subgroup of 7 patients with CFS seroconverted to EBV, while 24 patients with CFS for several months still lacked EBNA antibodies but had EBV-VCA antibodies (Table 6). This small group of patients representing approximately 10% of patients with the diagnosis of CFS from across Canada would deserve further studies and follow-up. Finally, only 2 of 27 patients with CFS and EBV-EA antibodies above 1:100 had IgG-1 serum levels slightly above normal adult values (Table 7).

An anomalous EBV-EA and EBNA antibody response has been previously described in a small subset of patients with CFS[6,7] and in patients with chronic active EBV infection[3,4,5]. The clinical significance and diagnostic utility of these findings are controversial since symptoms and signs of CFS may be found in just as many patients without EBV-EA antibodies[8]. An increased level of circulating IgG-1 has been observed in patients with infectious mononucleosis[9], Burkitt's lymphoma and nasopharyngeal carcinoma[10], and with chronic active EBV infection[4], but not in patients with CFS to our knowledge.

In conclusion, EBV reactivation may be slightly more frequent for as yet unknown reasons in some patients with CFS. In addition, a very small group (10%) of patients with the diagnosis of CFS appear to have a delayed or even possibly absent EBNA antibody response and would deserve careful follow-up as well as specialized immunologic studies.

Table 5.
EBV-EA Antibodies in CFS and Controls

	EA<10	EA≥10
CFS	187	91 (32.7%)
Controls	1454	329 (18.4%)

Table 6.
Chronic Fatigue Syndrome (CFS) Patients' Serologic Response

	EBV-VCA Positive	
EBV Seroconversion	EBNA neg ≤10, EA pos≥10	EBNA neg ≤10, EA neg≤10
7	9	15

Table 7.
IgG-1 in Patients with CFS and EBV-EA Antibodies ≥1:100

No. of patients	No. with Elevated IgG-1	Level of IgG-1
27	2	12.1 g/L 12.5 g/L

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12. Immunodysregulation and Chronic Fatigue Syndrome

S.K. Kundu, G.A. Ahronheim, J. Menezes

Introduction

Chronic fatigue syndrome (CFS) is a multi-system complex of diverse symptoms with impressively few objective signs or laboratory correlations agreed upon to date[1,2]. The etiology of CFS is not known. A satisfactory diagnostic test does not exist. Clinical case definitions created for the purpose of developing scientific understanding are often not useful for the diagnosis of an individual case[3,4].

Numerous infectious agents have been associated with CFS, including herpes-group viruses, enteroviruses, parvoviruses, measles and others. For example, much attention has been paid to the Epstein-Barr virus (EBV, a herpes virus), the causative agent of infectious mononucleosis (IM). Chronic fatigue syndrome is often reported to develop following an episode of IM or a mononucleosis-like illness, and profiles of antibodies to certain EBV antigens in some CFS patients resemble those observed in patients with persistent or reactivated EBV infections[5,6]. Some viruses, in particular measles and members of the herpes group, are known to interfere with host cellular immunity as part of their pathogenesis[7]. One might speculate that these viruses could, thorough their transient immunosuppressive actions, induce reactivation of latent viral infections.

A variety of abnormalities of cellular immune function have been described in CFS patients[3,8-13]. Although no one of these abnormalities is specific, taken together they suggest the existence of a genuine immune disturbance in CFS. Our hypothesis is that these immune abnormalities reflect a disturbance of immune regulatory pathways. Two major CD8+ T-cell subsets of the regulatory network are the suppressor (T_s) and contrasuppressor (T_{cs}) populations. Contrasupressor cells can be separated by their property of adherence to the lectin *Vicia villosa* (VV)[14]. Helper T-cells (T_h) are the principal immune effector subset, producing various lymphokines such as interferon gamma (IFN) and interleukin-2 (IL-2) which enhance natural-killer (NK) and other cytotoxic mechanisms[15-17]. Supressors down regulate $T\text{-}_h$ activity and $T\text{-}_{cs}$ counteract this downregulation[18], maintaining immune homeostasis.

Investigations and Observations

We have studied cellular immunoregulation in 7 subjects, aged 17-39 years, with CFS-like illness (and no evidence for other disease) during both remission and exacerbation periods, and compared them to a group of healthy controls. Peripheral blood mononuclear cells (PBMC) were evaluated for lymphocyte phenotypes, T_s, T_{cs}, NK and activated NK activity, and XIJN and IL-2 production.

Peripheral lymphocyte phenotypes were characterized using commercial monoclonal antibodies and flow cytometry. No consistent perturbation of subpopulations was apparent in CFS subjects, nor were there noticeable differences between exacerbation and remission patterns. The CD4:CD8 ratios were somewhat depressed in 6 of the 7 subjects (mean 1.4 ± 0.9); for the controls the mean was 2.0 ± 0.5.

Supressor cells were evaluated by their ability to suppress *in vitro* production of Immunoglobulin M (IgM) antibody by B-cells. Supressor activity was markedly increased in CFS subjects during exacerbation, less so during remission but still significantly more than that observed in the controls. Contrasuppressor activity, measured by the ability of CD8+/VV+ cells to counteract T_s suppression of *in vitro* IgM production, was decreased in symptomatic subjects but rose to levels higher than controls during remission.

Natural-killer activity in PBMC was measured with a standard cytotoxicity assay measuring ^{51}Chromium release from K-562 target cells[19]. Activated NK cytotoxicity was measured by preincubating the PBMC with soluble staphylococcal protein-A (SpA) and then measuring cytotoxicity against NK-resistant Raji cells. Supernatants of these cultures were assayed for IL-2 and XIFN. Natural-killer activity in subjects with CFS exacerbation was decreased as compared to remission and to controls; remission NK activity was slightly but not significantly decreased relative to controls. Activated NK cytotoxicity in CFS subjects was not apparently different from controls, during either remission or exacerbation.

XIFN and IL-2 production by PBMC stimulated by SpA was decreased in CFS subjects during exacerbation compared to controls. During remission IFNg and IL-2 production increased significantly to near control levels.

All our subjects had evidence of prior EBV infection, with antibody to EBV capsid (VCA) and nuclear (EBNA) antigens; in addition, 3 had low levels of IgM to VCA, 4 had low levels of antibody to early antigen (EA), and 2 had moderately elevated anti-EA. Controls were all anti-VCA and anti-EBNA positive, and IgM and anti-EA negative.

Discussion

The symptoms and clinical findings in CFS can be interpreted as suggestive of an incompletely resolved infection and/or of persistent immunological perturbation. In either case, an immunologic approach should contribute useful information. Our preliminary findings substantiate previous reports of immunologic derangements in CFS patients, extending our knowledge to the level of immunoregulation. The demonstration of immune dysregulation does not in itself indicate that the primary cause of CFS is necessarily immunologic in origin, and does not exclude infectious or other causes.

Our observations must be interpreted with caution. First, it is by no means certain that all seven subjects have the same disease process. To a greater or lesser extent they satisfy one or another clinical case definitions for CFS. The absence of a known etiology or an objective marker for CFS limits the precision of choice of subjects and controls[2-4].

Second, measures of lymphocyte function may vary in diverse physiological states, and may vary during minor illnesses. Thus changes are

usually not specific and must be interpreted in context.

Third, although many CFS patients, including some of ours, have serologic profiles for EBV compatible with active EBV infection, a primary role for EBV is still considered unlikely. Despite the widely-reported serologic association of EBV with CFS, there is little or no evidence that EBV has an etiologic role in the pathogenesis of most cases of CFS[4,20]. There are many clinically indistinguishable CFS patients among whom can be found some with perturbed EBV antibody profiles, some with profiles compatible with long-past EBV infection (i.e., the normal pattern found in >90% of North American adults: anti-VCA+, anti-EBNA+, anti-EA negative), and occasional ones with no evidence of prior EBV infection. Unlike the usually available serologic studies for most viruses, the availability of several EBV antigen-antibody test systems facilitates a sophisticated probing of the immunologic response to EBV. It is likely that the EBV antibody abnormalities reflect the disturbance of immunoregulation rather than active EBV infection. EBV serology may be useful to show evidence of a subtle immmunoperturbation but its usefulness in the evaluation of CFS patients remains controversial.

Acknowledgements

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13. Virology Laboratory Diagnosis of Chronic Fatigue Syndrome

B. McLaughlin

The Virology Laboratory of the Laboratory Services Branch, Ontario Ministry of Health, is in a somewhat unique position. The facility is a large laboratory providing services to a province of 9,500,000 inhabitants. It is the only virology laboratory except for six teaching hospitals, which test mostly their own patients, and one of only two laboratories testing for Epstein-Barr virus (EBV).

As previous speakers have discussed virology laboratory findings of different viruses in chronic fatigue syndrome (CFS), to avoid repetition, I will look at our global numbers and at the trends we have observed in our population over the last 9 years. Data on 2 types of viruses, EBV and enteroviruses, will be reviewed.

Epstein-Barr Virus (EBV)

Tests done in the last 9 years show a steady increase in demand for EBV testing (Table 1), with a cumulative total of 138,646 specimens. These vary with the age of the population tested and significant titres vary with the laboratory doing the test. We use a standard immunofluorescence technique, with a commercial kit for viral capsid antigen (VCA)-IgG, and prepare our own slides for the other markers. Viral capsid antigen-IgG is assayed at dilutions 1/80 to 1/640 (in children, the starting dilution is 1/20). Early antigen (EA) (R & D) are screened at dilution 1/40, as this is the dilution at which we found clinical and statistical differences.

Roughly 80% of the tests we receive are from adults, and more than 99% of adults over 39 years of age are VCA-IgG positive. For this reason the tests chosen for adults are VCA-IgG and EA (EBNA) and VCA Immunoglobulin M (IgM) are done mostly in children and teenagers, where primary infections are suspected.

We consider an EA ≥40 to indicate a recent, or relatively recent active infection (primary or reactivation); a VCA ≥640 with EA <40, a relatively recent active infection but less recent; positive VCA-IgMs have been positive only rarely in our adults; EBNAs have been almost constantly positive in adults, indicating those high VCAs or present EAs were due to reactivations. It is very difficult to interpret EBV serology significance in cases with "fatigue" of more than six months' duration, or of several years' duration.

Figure 1 shows the large, steady increase in demand for the test. The media's influence on demand has been very noticeable following programs on TV and radio, and publications in popular magazines and newspapers on chronic fatigue, chronic EBV infections, the "Yuppie Plague," "Lake Tahoe Disease," etc.

If we look at the *percentage* of significant results (Figure 1), we see that specimens with VCA ≥640 with EA <40, and specimens with EA ≥40 represent about equal numbers in 1983-84. The percentage of EA ≥40 increases while the EA <40 decreases in 1984, 1985, 1986, and 1987. In 1988-89 (Table 2), they are restored to the proportions of 1983-84. It seems that between 1983 and 1988 the number of recent reactivations was higher. Although it is impossible to draw accurate conclusions from such data, it seems that some event occurred between 1983 and 1988 to cause EBV reactivations.

Enteroviruses

Dr. Byron Hyde has earlier discussed the etiologic significance of polio, coxsackie and echoviruses as causes of CFS. We reviewed the enteroviruses diagnosed in our laboratory during the last 9 years. A total of 3,225 (Table 3) diagnoses were made. These are virus diagnoses made by isolating viruses in cell cultures while some were detected only by electron microscopy. They represent mostly cases of viral meningitis, "summer flu," sore throat, fever, myalgia, pleurodymia, febrile rashes, and diarrhea, and they were essentially detected in late summer and early winter. Typing of these enteroviruses is time-consuming and was not always done, but we see a peak of Coxsackie B5 in 1984-85 and Echovirus 7 in 1986-87.

Figure 2 shows the increase in enterovirus detection between 1984 and 1987, with a decline in 1987-88. Enteroviruses are always present in Ontario, with type variations and epidemic peaks varying from year to

Table 1.
EBV Serology of Ontario Patients: A Nine-Year Review

	Total Tested	VCA+ EA≥40	VCA≥640 EA<40	Sero-Conversions	IgM VCA+
1981-82	11,492	1,676			
1982-83	7,419	2,688			
1983-84	7,878	1,540	1,652		
1984-85	10,600	3,499	1,953		
1985-86	16,835	4,335	2,706		
1986-87	22,409	5,193	2,633	39	31
1987-88	33,734	6,984	5,292	42	16
1988-89	28,669	5,193	4,891	56	59
	138,646				

Figure 1
EBV Serology: Nine-Year Period
(138,646 specimens)

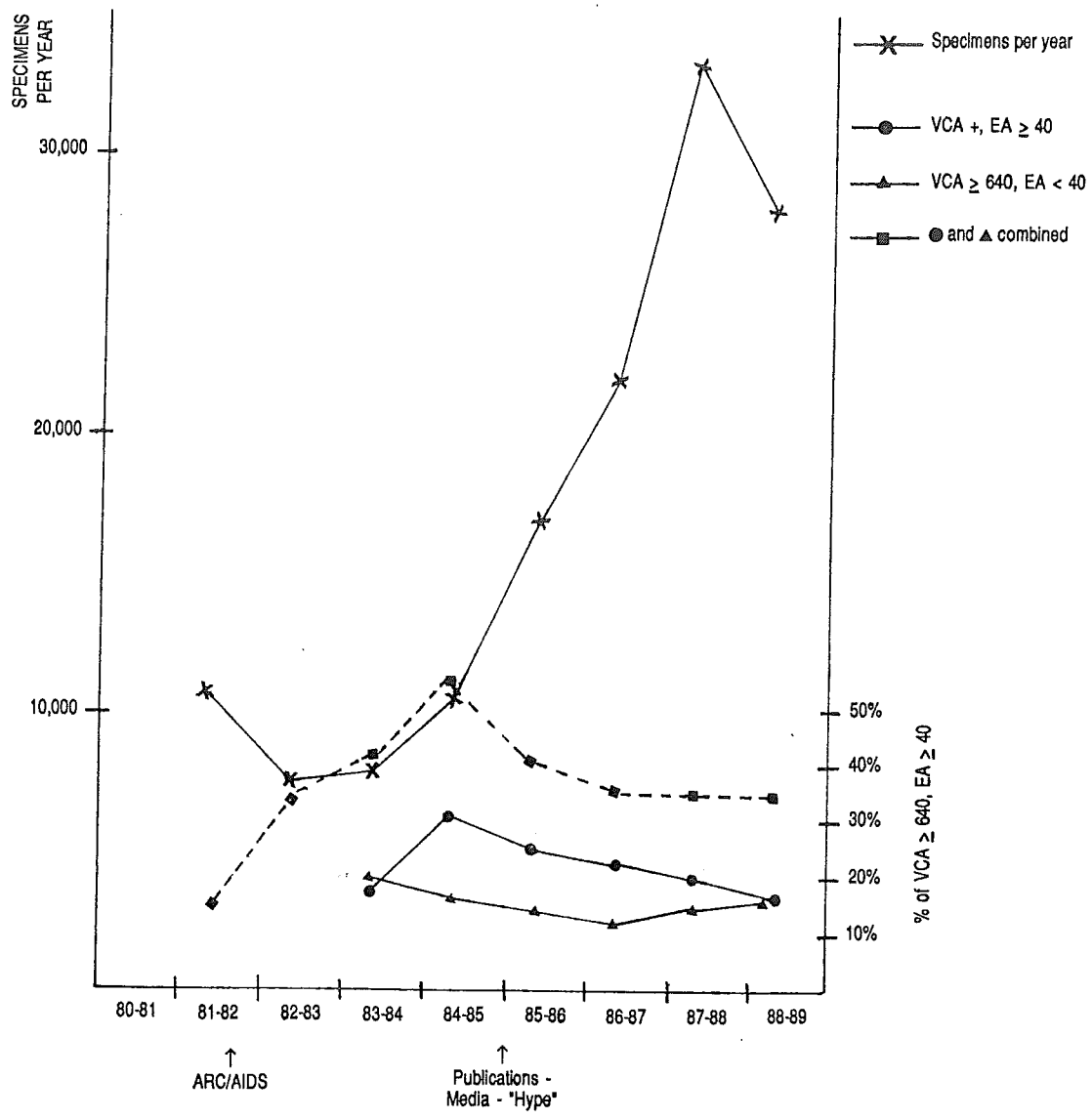

Table 2.
EBV Serology of Ontario Patients: March, April, May 1989

Age	VCA<40 EA<40	40-320 128<40	≥640 <40	40-320 ≥40	≥640 ≥40	Sero-Conversions	IgM	Total
≤14	232	180	47	10	29	2	3	503
15-20	150	341	109	33	49	3	4	689
21-25	50	274	75	22	38	0	0	459
26-30	39	325	130	40	78	0	0	612
31-35	36	273	132	40	73	0	1	555
36-40	19	218	123	41	90	1	0	492
>40	64	583	284	83	177	1	0	1,192
Total	**687**	**2,605**	**1,095**	**309**	**662**	**7**	**8**	**5,373**
%	12.7%	48.4%	20.3%	5.7%	12.3%	0.1%		

Table 3.
Nine Years of Enterovirus Isolation Results from Ontario Patients

				80/81	81/82	82/83	83/84	84/85	85/86	86/87	87/88	88/89	Total
C	V.	Coxs	A,nt	5			6						11
o	I.	Coxs	A 9	14	6	14	8	13	18	7	21		101
m	&	Coxs	B 1				3				1		4
b	S.		B 2	9	14	4	10	17	11	1	4	3	73
i			B 3	31	2	13	6	28	10	3	17	4	114
n			B 4	30	15	36	13	27	3	1	8		133
e			B 5	6	8	2	22	160	1	1	3	4	207
d			B 6			1							1
				95	**45**	**70**	**68**	**245**	**43**	**13**	**54**	**11**	**644**
		Echo 2					1					1	2
		3			3	2	1		2	5			13
		5			3			43			2	5	53
		6		2	3	3	1	7	1		5	1	23
C	V.	7		1					6	71		1	79
o	I.	9		5	1	2	11	13	22	6	10	2	72
m	&	11		8	5	4	25	15	23	18	6	1	105
b	S.	13			1								1
i		14				1	1	1		2	5		10
n		17		2	1		5						8
e		18									6		6
d		21		3									3
		22							10				10
		24					1		2				3
		25					1						1
		29		1								1	2
		30				5	7	8					20
				22	**17**	**17**	**54**	**87**	**66**	**102**	**34**	**12**	**411**
V.	o	Polio 1				1,v						1,w	2
I.	n	2		1,v		1,v		2,v					4
	l	3			4,v	6,v	2,v						12
	y												
				1	**4**	**8**	**2**	**2**	**0**	**0**	**1**	**1,v**	**19 (1w,18v)**
V.	o	EM Only							99	266	90	111	566
I.	n			124	172	109	138	78					621
	l	Ent, nt							149	290	321	192	952
	y												
				124	**172**	**109**	**135**	**78**	**248**	**556**	**411**	**303**	**2,139**
		TOTAL		**242**	**238**	**204**	**262**	**412**	**361**	**671**	**500**	**327**	**3,225**

Legend
nt = not typed
v = vaccinal
w = wild

Figure 2
Enteroviruses Isolation and Serologic Diagnostic Results (3,225 viruses) Over Nine Years from Ontario Patients

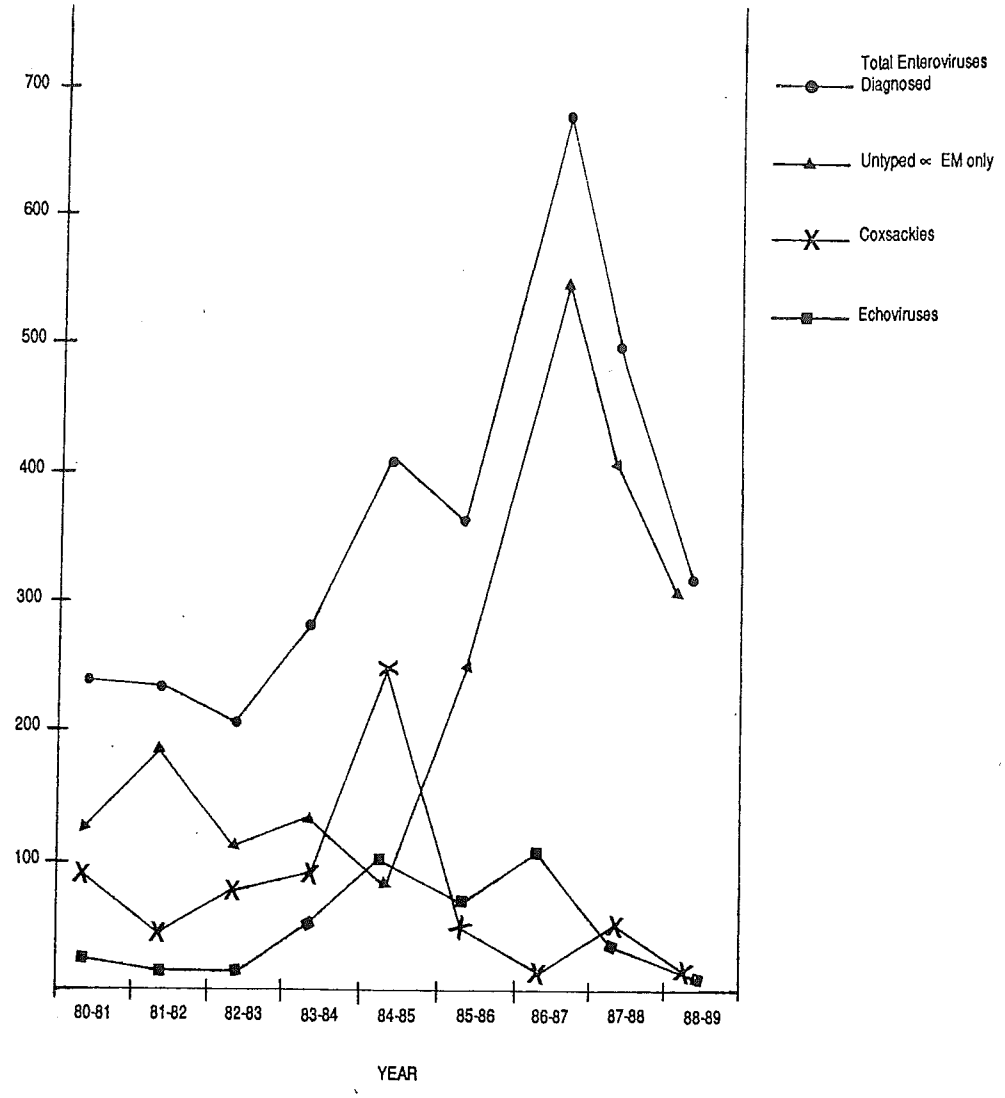

Table 4.
Chronic Fatigue/Myalgic Encephalomyelitis Enterovirus Serology January – June 1989

High Titres to 1 or 2 Viruses (≥1:512)

Polio 1	1
Polio 2	3
Polio 3	18
Coxsackie B2	1
Coxsackie B3	3
Coxsackie B4	3
Echovirus 9	1
	30
Total Tested	1269
% with High Titres	11%

year, which again makes interpretation of these data difficult. Serology for polio and coxsackie in patients said to be suffering with CFS was analyzed for the first 6 months of 1989 and showed frequently high titres for polio, especially Polio 3 (Table 4). The results are difficult to interpret in the absence of precise clinical or immunization history, which we were unable to collect.

Discussion

The laboratory data reviewed here are of 2 different types. For EBV, the number of specimens received were certainly influenced by the media, and the percentage of significant results were provided by the laboratory. For enteroviruses, the number of actual viral isolates from clinical specimens should not have been influenced by media "hype" but should reflect the epidemiologic patterns of these viruses. Still, both EBV reactivations and enteroviruses infections increased between 1983 and 1987, a phenomenon that seems to confirm the impressions of Dr. Mildon and Dr. Hyde in their review of their Ontario patients. It is impossible to draw further conclusions from these very general data, but they do merit further investigation.

14. Summary — Session C

K. Rozee

Summary

It was noted that there are unfortunately no laboratory tests available at present to confirm or exclude the diagnosis of CFS. Such objective markers of the syndrome are urgently needed. However, a very small subset of patients with CFS display abnormalities in their antibody response to EBV and/or nonspecific abnormalities of the immune response. Drs. McLaughlin and Joncas described the former while Dr. Menezes discussed the latter. The abnormalities in EBV antibody response involve either antibodies against the early antigen or the nuclear antigen of EBV infected cells; the titre of EA antibodies rise above 1/100 and persist longer at that level and/or EBNA antibodies remain persistently absent or at extremely low titres. One or other phenomenon, particularly when it occurs in the rare patient who goes on to develop a syndrome of chronic fatigue following a proven primary EBV infection with infectious mononucleosis, suggests a cause and effect relationship. A concomitant rise in 1985 in the incidence of EBV and enterovirus infections noted by Dr. McLaughlin may only be coincidental although an interaction between the 2 viruses or group of viruses mediated by transactivating proteins from one or the other virus cannot be excluded. Dr. Menezes stressed the possible value on a research basis of a few immunologic tests that have been shown to be abnormal in a subset of patients with CFS such as NK cytotoxicity, blast transformation tests with mitogens, levels of interferon y, IL-1 and 2, circulating immune complexes, and T-lymphocyte subpopulations including T-contrasuppressor activity.

Session D
Definition

15. Definition of the Syndrome and Differential Diagnosis

A. Komaroff and J.H. Joncas

Joncas: We have arrived at the time when we must put to use the previous discussion. For my own self, a working case definition is in the nature of an hypothesis to be validated.

Salit: The case definition that is current, that of Holmes, is ambiguous with respect to the important feature of chronic psychiatric disease and its exclusion from chronic fatigue syndrome (CFS).

Joncas: This is true, and there is also the question of malingering. These are 2 important exclusions and I wonder if Dr. Cooke could help us. Can these be sufficiently well diagnosed so that they could be excluded?

Cooke: Major depressive disorders have many distinguishing features but CFS is not as well defined as yet. To distinguish the two may be difficult. Dr. Hyde suggested a good rule for excluding patients with a history of depression and psychiatric history.

Komaroff: The Centers for Disease Control (CDC) (Holmes) definition is ambiguous with respect to the exclusion of those with affective disorders occurring prior to their CFS. What is a case definition useful for? It seems important to me that **we should agree on a set of data that we all collect when the patients arrive with possible CFS so that we can eventually define an adequate case definition.**

Ablashi: The CDC (Holmes) definition was made in 1985 and we have more experience now. We should be able to define it better.

Komaroff: Dr. Cooke, can we decide on psychiatric grounds whether or not a major affective disorder had occurred prior to CFS?

Cooke: Not easily, if at all.

Hyde: Of course, we have to look at all the possible CFS patients, but we have to put into another subgroup those with a previous psychiatric history of affective disorders. This is not a new argument but has been applied in many diseases, even paralytic poliomyelitis.

Joncas: Can we put patients with a previously diagnosed psychiatric history into a subgroup of CFS?

Salit: I agree. CFS, Type 1 – no prior illness; Type 2 – prior major affective disorder and depression.

Sekla: Why is a period of 6 months with a health problem needed?

Komaroff: We need this to exclude those who would recover normally from infective illness. Many patients recover normally with some delay.

Joncas: Can we exclude malingering, Dr. Cooke?

Cooke: A neurologist probably can do a better job than a psychiatrist. I think it would be difficult.

Salit: Most malingering is not malingering but just another psychiatric illness. It is not CFS and we should exclude such patients if we can, but the patient is probably incapable of working anyway.

Ahronheim: We must be clear about our 2 jobs. One is to get a case definition for research purposes, but the second is to help us function as clinicians in our patients' best interest.

Joncas: What about burn-out? Can we distinguish it from CFS?

Komaroff: There is no case definition of burn-out either.

Salit: There is no need to differentiate since the patient is unable to work anyway. The question is redundant.

Komaroff: The point is that burn-out is probably a major depressive illness, not CFS as we want to define it.

Joncas: Let's leave exclusion criteria and go to inclusive criteria.

Salit: The CDC (Holmes) case definition mentions no laboratory tests. We should consider this question.

Purtilo: Dr. Komaroff mentioned that the posterior cervical nodes (PCN) were positive in 35% of his CFS patients. Is this a sign we should consider?

Komaroff: We are now comparing the PCN+ group with others in our CFS group to see if they differ in other ways. We can't say yet.

Joncas: Intolerance to alcohol and other drugs seems to be important. Can we consider this?

Komaroff: Fifty to 55% are intolerant and this percentage is not enough for differentiation (but may be important, if other criteria suggest CFS [ed.]).

Joncas: Objective measures of muscular pain and weakness were mentioned as being important. Can we consider these measures?

Komaroff: There are 15 different ways to assess these parameters, with no really consistent findings. We have not made any comparisons as yet and cannot say.

Hyde: Many of these questions concerning whether or not certain features are diagnostic are unanswerable since they cover too wide a field. The term "chronic fatigue syndrome" was used as a garbage bag until the CDC (Holmes) definition and this just made the bag a bit smaller (but still a garbage bag [ed.]). We need to make it smaller still by defining the features more precisely.

Komaroff: I wonder whether we *can* make it smaller. We are reliving the lesson of history that it takes a long time to identify an objective marker to define a particular syndrome precisely.

Ahronheim: Can we, for research purposes if not for diagnostic ones, at least be more definitive?

Komaroff: Not unless you want to be more precise about the features of CFS you want to study.

Ahronheim: We do have some exclusion criteria that are helpful, for example, the requirement that the illness be of 6 months' duration, and prior to psychiatric illness.

Joncas: Drug intolerance, particularly alcohol, is also interesting and should be a subject of research. Also pertinent to our discussion: what metabolic problems do CFS patients have? Can we use an alcohol tolerance test to include or exclude patients from our CFS group?

Hyde: CDC (Holmes) is too broad for a working clinical diagnosis. The disease must be phased. In my view, these are: Phase 1 (initial), Phase 2 (partial recovery), and Phase 3 (chronic, prolonged, gradually debilitating illness).

Joncas: That is probably correct, but requires more research. You will note that I used the phasing in the model I presented yesterday.

Hyde: Can we submit our working case definition for publication without a thorough discussion of this aspect?

Purtilo: Dr. Komaroff, give us a prototypic description.

Komaroff: There is an acute initial phase lasting 3-6 months which is the worst phase of the illness, then a period of improvement lasting 3-12 months, then a very variable course of ups and downs thereafter, most showing very considerable recovery.

Salit: In our group the acute phase, which is also the worst, lasts 3-6 months; then patients realizing they must change their lifestyle begin to improve over 6-12 months. There is a slow improvement over several years. Virtually all improve to a more functional level, but very few go back to what they consider "normal." In my view, there is no inexorable downhill course.

Purtilo: This seems like a delayed recovery from a normal infectious disease. Pathologists have told us that a viral illness takes 3-6 months for the recovery phase (for tissues and systems to return to normal [ed.]). You may be selecting a subset of these persons whose recovery phase just features particularly unfortunate and rare symptoms that delay their recovery.

Hyde: Are Dr. Salit's patients depressed?

Salit: Yes, and they run a very variable depressive course.

Cooke: Drug intolerance may be an interesting and definitive feature, if we could explore it further.

Komaroff: I have never seen a young adult who was intolerant, but it certainly occurs in those young adults with CFS.

Joncas: I believe we have reached a consensus on how we can define a working definition of CFS.

Jain: Is the suggestion that we will then divide CFS into 2 groups, one having no prior psychiatric history? (Ed.: There was consensus on this point.)

Abbey: The Diagnostic Interview Schedule (DIS) is very important in evaluating a prior history. Currently, we use this and we need this or something else that includes all the symptoms.

Komaroff: Could we use another Depression Index so that clinicians could avoid the use of the lengthy DIS instrument?

Abbey: Yes, there are many good clinical check lists. The DIS was designed for lay administration but clinicians usually administer other check lists to avoid the use of a long interview instrument. Many are very good tools.

Cooke: The choice should be appropriate to the setting. DIS, SKID, and SADS are all good.

Joncas: Can we suggest one?

Abbey / Cooke: All of the ones we use follow the American Psychiatric Association's criteria for major depressive episodes published in the Diagnostic and Statistical Manual of Mental Disorders [DSM-III-R (revised version of the 3rd. ed.)].

Komaroff We should publish the 15 items in DSM-III-R as a reminder. (Ed.: These items are published here in Appendix A.)

Joncas: Perhaps Dr. Salit or Dr. Komaroff can tell us the number of patients with clearcut CFS with no major affective disorders.

Salit: There are about 25% of patients in our experience.

Komaroff: We should define those with pre-existing major affective disorders prior to CFS and those whose CFS includes a major affective disorder.

Joncas: That's right, we need to include both. It will then be Type 1 – clearcut CFS with no pre-existing or co-existing psychiatric illness and Type 2 – CFS with (a) pre-existing or (b) concurrent major affective disorder, alcoholism, or symptoms meeting the criteria as defined by DSM-III-R of the American Psychiatric Association for major depressive episodes.

Joncas: I think we must exclude those persons with other chronic diseases and not include them as CFS, Type 3 group.

Hyde: I still think there will be a third group that is so complicated in history that its members do not fit into CFS type 1 or CFS type 2 (a) or (b).

Komaroff: I agree that there is this third group but in a formal case definition we cannot include it. We clearly must treat these patients but not as having CFS as defined in our case definition, for all the reasons you gave previously for making the garbage bag smaller.

Session E
Recommendations

16. Recommendations for Laboratory Investigations and Symptomatic Treatment

I.E. Salit and B. McLaughlin

Salit: Perhaps we can consider the use of laboratory tests first. I take it that what we are considering here are tests that can be useful for the practising physician to evaluate his patients rather than in the research sense. Dr. Komaroff, what tests would you suggest?

Komaroff: CBC but with a manual differential to detect atypical cells; sediment rate; chemistry panel; assay for immune complexes.

Salit: This assay is usually not readily available in Canada.

Komaroff: Total immunoglobulin levels. Only the IgG and IgM have been useful in that they are higher in CFS patients than in normal ones; ANA; rheumatoid factor; TsH; thyroid antibodies to antimicrosomal antigens.
I think this is a reasonable list for the practising physician, but there is a set of other tests, such as X-ray for an existing cough, that should be based on specific symptoms.

Joncas: I am surprised that you have excluded Epstein-Barr virus (EBV) antibodies. Although not all CFS cases are EBV-infected, at least when it is positive it defines a known subset of CFS.

Salit: The question usually is, if you see them 6 months after the infection, EBV antibody analysis is not understood or very helpful to the average physician.

Joncas: What about a subgroup with no EBNA with VCA antibodies, especially for research purposes.

Salit: I thought we were focusing on the general practitioner and not our research groups. I think we have to keep this in mind with our recommendations.

McLaughlin: It is true that we will do more laboratory work for patients in research-based studies but we should do some laboratory tests once the CFS diagnosis is established in patients, even those from general practice. (This will add essential data to our database referred to earlier [ed.].)

Salit: I am reminded of a person looking for car keys under a street light. When asked by his friend why he was looking there for them when he lost them across the street, he replied that the light was better on this side.

Joncas: I agree that EBV serology means that it is a lot of work to identify a very few patients with EBV disease.

Salit: Can the diagnostic laboratories handle an additional 25,000 more EBNA per year? Is it justified? I don't think so.

Joncas: Perhaps not; perhaps it may not find its way into recommendations, but for the investigation of EBV-based CFS it is essential.

Comment from the floor: Why not exclude coxsackie A investigation or other virus serology by the same argument?

Salit: Do we agree that for those in general practice virus serology for CFS may not be useful?

Ahronheim: Generally, but we do a human immunodeficiency virus (HIV) test for putative CFS. We believe it is an important exclusion test.

Ablashi: I would prefer to do HTLV-I serology.

Lee: Do you ask for the patient's agreement?

Ahronheim: Yes. I put it very simply and I have never had a problem.

Hyde: Some of these tests are not of value for CFS but may find a place in the patient's workup in other respects or in a research setting.

Sekla: Why look for atypical lymphocytes?

Komaroff: This provides data for an important differential analysis in my view.

Mildon: Malignant hyperthermia is turning up in CFS patients in my practice. We must differentiate these persons as it is a life-threatening disease.

Salit: We must remember that we are trying to recommend what the practising physician should routinely do. Serologic tests for viruses at a late date are not usually of value or to be recommended as being of major benefit.

Ahronheim: Acute Toxoplasma has many features in common with CFS.

Salit: We only have 2 that went to CFS. Although there is much CFS among patients at our Tropical Medicine Clinic, acute *Toxoplasma* is not found very frequently in CFS.

Hyde: This disease is difficult to diagnose clinically, if you have not seen a large number of cases. It becomes much easier if you have, even in the absence of an objective marker. We should recommend to physicians in any community that one of them should specialize in this disease.

Salit: I do not think that that suggestion would be helpful. I value the opinion of a variety of physicians looking at the patients. I think the relative non-value of viral serology should be emphasized, except in certain research circumstances. The practising physician does not require these particulars at such a distance from the infection.

Joncas: We have to retain serologic and other laboratory tests for research purposes, especially for the EBV subgroup.

Ablashi: If this recommendation excludes the recruitment of patients from practising physicians, how do we gather patients for our research studies? We will have to make special arrangements with certain practices.

Salit: Obviously we must not close the door to these research efforts, but in general we should recommend against viral serology for the usual practising physician.

Hyde: Fifty percent of our patients show an increased 24-hour creatinine clearance test. We do this test as a marker of muscle breakdown.

Salit: But that is a test for function; a rate.

Komaroff: I wonder whether many of these tests are of value. We have to be careful of outliers in the normal group. The normal value found in tests of normal values usually does not establish the *range* of quite normal values. Some of our studies have identified this problem.

Salit: Could we turn now to symptomatic treatment? The approach I use is to carefully explain the nature of the illness to our patients. Many have their minds eased by this method. Counselling is *very* important. It does not produce a dramatic cure but it makes the patient feel better, more able to cope. Symptomatic treatment of sleep disorder and antidepressants are also used in our CFS patients and patients who can stay on antidepressants feel much better.

Hyde: Most of our patients cannot tolerate antidepressants.

Abbey: Reassurance is very important to CFS patients and the general physician should be told that CFS patients are very sensitive to antidepressants. Low-dose antidepressants are the rule, and this is very characteristic of tricyclic antidepressants in CFS patients.

Mildon: Dietary restriction problems with antidepressants are sometimes overrated.

Ahronehim: Have any drugs made depression greater? I mean, have they increased the patient's anxiety or depressive state?

Komaroff: Some of our patients have become very agitated on some drugs.

Hyde: There are several new drugs being used, Ca channel-blockers and antiepileptic drugs. We are in the infancy of drug therapy.

Joncas: Have any placebo studies been done?

Komaroff: Acyclovir is the only controlled study to be done to my knowledge.

Ahronheim: Have any analgesic studies been done?

Komaroff: Non-steroidal analgesics are of benefit in arthralgias. They are quite useful and could be recommended.

Hyde: Problems of "health-food" remedies must be recognized, especially those called "natural" by the advertisers.

Salit: I agree. They are expensive and sometimes dangerous; some patients who refuse "medication" do not consider so-called natural remedies as "medication" and are very susceptible to being taken in by quackery.

Session F
Research Avenues

17. Avenues for Research in Chronic Fatigue Syndrome Etiology

J. Menezes and D.V. Ablashi

Ablashi: We suggest that we consider this topic under 3 headings: (1) virologic investigation, (2) immunologic investigation, and (3) metabolic aspects. In our own experience we have investigated CFS patients for serologic conversion following virus infections by long-term follow-up.
In our human herpesvirus 6 (HHV6) studies with Dr. Purtilo we are looking for distinctive markers with which to characterize CFS. We are also interested in the use of phosphonoformate following our *in vitro* study of HHV6 sensitivity to this drug.

Salit: We have about 20 acquired immunodeficiency syndrome (AIDS) patients on this drug but I do not think the blood levels are as high as those in your *in vitro* studies. We must realize that this drug has toxicity.

Joncas: Phosphonoformate blood levels are lower than the effective *in vitro* antiviral concentration. It is quite toxic.

Rossier: In any etiology study we have to avoid the pitfall of 1 organism equals 1 disease. This cannot be the case with CFS.

Sekla: Does anybody use antibiotics for CFS?

Salit: Much experience has shown antibiotics are of no value and the general physician should resist pressures by the patient to prescribe them.

Ahronheim: We need to arrange for proper banking of specimens, serums, etc. from defined CFS cases to facilitate future research. This is essential.

Ablashi: You are right. This aspect is essential and it has been improved greatly since we have had a proper case definition.

Cooke: Is there concern about Borna virus? Is it important?

Salit: It is just another virus to worry about!

Menezes: Can we move on to immunologic abnormalities? It may be important to phenotype well-defined CFS patients. Our opinion is that NK cell activity is also an important parameter to be measured in CFS. This is a good measure of the CMI competence of CFS patients.

Hyde: Are there any clinical laboratories that do these tests as a routine for the practising physician?

Ablashi: Probably not. It is a research laboratory technique.

Hyde: This represents a problem to the clinician. It is not very helpful if you cannot obtain these tests in general practice.

Menezes: Assays of NK cell activity are a measure of response to non-self antigens and as such are a valuable parameter of measurement in CSF.

Hyde: What would it cost to run a study of NK cell activity in a group of patients?

Menezes: This is difficult and would depend on the study. I could let you know, if you wished to provide the details of the proposed study.
Selective analysis of cytokines would also be important – I11, I12, and IFN particularly.
Mitogen stimulation, autoantibodies, and blocking factors should also be considered as important parameters. This is a vast field which requires some major efforts to establish priorities.

Lee: Antigenic stimulation rather than mitogen stimulation may be more revealing. You could choose specific viral antigens to try and define the causative agent.

Salit: We looked at some of our patients in this way by testing tetanus toxoid/ strep/CMV/herpes1/mumps antigens by stimulation of PBMCs. Forty percent had poor response to 2 of the above but no correlation seemed to occur. We consider these to be very soft data and probably another panel may be better. This was a fishing expedition.

Joncas: Bioassays on patients' PBMC have great variability and this would have to be controlled. This type of study is very difficult to do properly.

Middleton: Is testing for 25A synthetase useful?

Salit: It is not useful. Only 40% of CFS patients have an elevated synthetase.

Menezes: Let's go to the third part, that of the metabolic aspects.

Hyde: Is there anyone in the government or the granting agencies who would fund these studies?

Ablashi: Perhaps Dr. Rozee could comment later. Also, can we organize formal epidemiologic studies to look at environmental or metabolic factors? Both of these are required for definite answers.

Joncas: There may be a common factor that could be identified between intolerance to drugs and alcohol and CFS related to metabolic deficits. We should look at allergic reactions. Also, enzymatic phenomena seem to be important here. Studies should be done to determine the importance of those.

Cooke: The intolerance to alcohol and drugs is probably a pharmacodynamic effect related to receptor density, as is sensitivity to allergens, rather than other effects related to the pharmacokinetics of these drugs.

Salit: I agree that it is probably receptor-based rather than drug dynamics, although most of our studies on metabolic parameters did not show any difference.

Ahronheim: This would be a good time to look at histamine receptors in these patients. The technology is available. Can I re-introduce the question of epidemiologic data collection based on patients who fall within the case definition we have suggested? We badly need valid studies of this nature to focus our efforts.

Ablashi: CDC now has a grant to do this in Atlanta. They have also prepared clinical summaries for distribution to practising physicians.

Menezes: If there are no other suggestions, we can ask Dr. Rozee to make a few concluding remarks.

18. General Remarks and Closing

K. Rozee

Thank you all for your efforts; it has been an intense 2 days.

The purpose of this workshop was twofold. First, we wanted to try to reach a *consensus* on what clinical, psychiatric, and laboratory parameters are thought to be important. If no consensus were possible, we sought *at least* to have as full a discussion as possible to help those with a diagnostic interest in CFS.

Secondly, we wanted to develop Proceedings that would be widely distributed as an *advisory* to the many Canadian physicians and laboratories that confront the diagnosis of this syndrome every day. We wanted an advisory that had the status of being provided by experts active in the field of CFS.

I think that we have accomplished the first. We have reached a workable consensus.

The second goal, that of developing and printing Advisory Proceedings, will be next on our agenda and I will contact you shortly.

Finally, I want to thank you all for taking time to come to Toronto and participate. I know how difficult it is to find such time but, believe me, it is appreciated.

Appendix A

*19. American Psychiatric Association Definition of Major Depression**

Definition

At least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood, or (2) loss of interest in pleasure. (Do not include symptoms that are clearly due to a physical condition, mood-incongruent delusions or hallucinations; incoherence, or marked loosening of associations.)

(1) Depressed mood (or can be irritable mood in children and adolescents) most of the day, nearly every day, as indicated by either subjective account or observation by others.

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation by others of apathy most of the time).

(3) Significant weight loss or weight gain when not dieting (e.g., more than 5% of body weight in a month), or decrease or increase in appetite nearly every day (in children, consider failure to make expected weight gains).

(4) Insomnia or hypersomnia nearly every day.

(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

(6) Fatigue or loss of energy nearly every day.

(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Exclusion Criteria

1. (1) It cannot be established that an organic factor initiated and maintained the disturbance.

   (2) The disturbance is not a normal reaction to the death of a loved one (Uncomplicated Bereavement).

   Note: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration suggest bereavement complicated by Major Depression.

2. At no time during the disturbance have there been delusions or hallucinations for as long as 2 weeks in the absence of prominent mood symptoms (i.e., before the mood symptoms developed or after they have remitted).

3. Not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS.

* Major depression as described in the *Diagnostic and statistical manual of mental disorders*. 3rd ed, revised. Washington, DC: American Psychiatric Association, 1987.

Appendix B

20. Workshop Recommendations on the Case Definition of Chronic Fatigue Syndrome and on Tests Useful to General Practitioners and for Special Purposes

From the Proceedings of our workshop we can abstract the following recommendations:

1. **Modifications to the case definition of Holmes et al. (Ann Intern Med 1988;108:387-9).**
   (1) We recommend that chronic fatigue syndrome (CFS) be considered as consisting of 2 types:

   Type 1 - CFS with no pre-existing or co-existing major depressive syndrome.

   Type 2 - CFS with (a) pre-existing or (b) concurrent major depressive syndrome as defined by the American Psychiatric Association (DSM-III-R).

   (2) It is the experience of the workshop that one-quarter to one-third of CFS patients will qualify as CFS Type 1.

   (3) We consider that, in addition, CFS is a triphasic syndrome:

   Phase 1- (lasting 3-6 months), an acute phase of greatest illness.

   Phase 2- (lasting 3-24 months), a phase of slow improvement.

   Phase 3- stability at an improved functional level usually subjectively less than 100% (no inexorable downhill course).

   (4) There is a third group of patients, typified by a complicated history, who do not meet all of the necessary criteria for CFS, although they may in fact fulfill some and have a major debilitating illness.

2. **Laboratory investigations that may be helpful in establishing a diagnosis of CFS.**
   (1) Differential tests useful for general practitioners
   (a) Peripheral blood *manual* differential for atypical lymphocytes
   (b) Sedimentation rate
   (c) Blood chemistry panel
   (d) Total immunoglobulin levels (IgG, IgM, IgA)
   (e) Antinuclear antibodies
   (f) Rheumatoid factor
   (g) Thyroid-stimulating hormone
   (h) Antibodies to thyroid microsomal antigens
   (i) Radiographs for existing respiratory problems or appropriate to disease in other organ systems.

   (2) Tests useful for special investigations and research purposes
   (a) The above list, *plus*
   (b) Immune complex assay
   (c) Virus serology focused on likely etiology as determined by history, i.e., Epstein-Barr virus (EBV), human herpesvirus 6 (HHV6), etc.
   (d) Special attention paid to drug sensitivities, especially alcohol and antidepressant intolerance
   (e) Measures of immune competence (i.e., NK cell activity).