

Chronic Fatigue Syndrome and its Connection to ADD/ADHD

Preface

After many delays, and revisions, this manuscript represents an attempt to summarize much of the background and current literature to date regarding this confusing phenomenon we call CFS/CFIDS and its potential connection to ADHD in children (and adults).

In writing this, I am attempting to help physicians, patients, educators and others further understand this complex phenomenon. I have attempted to separate what is “accepted” and/or verified by literature publications, versus my “opinions” and “positions.”

To all of you reading this, I hope this helps add some insight and understanding of the complex epiphenomena. To all of you who may have and are suffering with this illness, I hope you will soon see an acceleration of our clinical knowledge, such that successful treatment protocols are available in the near future for all.

The question is often asked, “What can be done as patients.” With recognition by our medical establishment of the legitimacy of this problem, they are encouragingly on a path to find answers to verify or disprove clinical opinions and further basic science, with an attitude significantly different from even a year ago. This author believes the critical need for patients (via hopefully corporate or private funding sources) is to accelerate steps that will “jump-start” controlled therapies, while our medical establishment searches for all the scientific answers.

I have said too many times over the years, that in spite of the complexities and uncertainties, there is an underlying logic that provides for common sense and potential treatments in the near future, providing for optimism rather than the ongoing pessimism one encounters. There are good reasons to be optimistic, we all have to make things happen - NOW.

Michael J. Goldberg, MD

Note: I wish to thank my wife and family. While I would never wish this illness/syndrome on any individuals, many times my wife and I have “kidded” about the involvement and progress I have made thanks to her developing this illness. Without my wife’s participation and help, most of my clinical research (in the midst of an ongoing Pediatric practice) would have been impossible. My children, have been more than understanding of the time required, along with helping edit and transcribe various projects and papers along the way.

INTRODUCTION

For the purpose of this paper, the terms CFS or CFIDS (Chronic Fatigue Immune Dysfunction Syndrome), the currently used and accepted nomenclature, will be

employed. However, it is the fervent hope of this writer that in the near future the existence of an immune dysfunctional/dysregulatory state will be commonly accepted, whether exhibiting fatigue or not, especially in the case of juvenile patients. Perhaps we will come to recognize that an immune dysregulatory state is a generalized condition which may include many inner related phenomena, such as CFS/CFIDS, atypical and/or typical rheumatoid disease, and probably, parts of ADHD, Autism (particularly in high-functioning or atypical patients), as well as other learning disabilities.

At the time of this writing, what we call “Chronic Fatigue Syndrome” is characterized primarily by chronic or recurrent debilitating fatigue combined with other symptoms. These symptoms include, but are not limited to, sore throat, lymph node pain and tenderness, headache, myalgia, arthralgias, and an impaired ability to concentrate, associated with short term memory loss. Sleep disruption, particularly a non-restorative sleep, has frequently been associated with this syndrome, as reported by other health professionals, as well as my personal clinical experience. Non-restorative sleep and cognitive dysfunction are frequently seen symptoms in children. During the last century this syndrome has had many different names (figure 1). Since 1985, the Division of Viral Diseases, Centers for Disease Control has responded to pronounced increases in requests for information about Chronic Fatigue Syndrome.

Because no single diagnostic test exists to define CFS/CFIDS, the current definition is based upon a combination of signs and symptoms only. According to the CDC’s “original” 1988 definition (figure 2), Chronic Fatigue Syndrome is an operational concept designed for research purposes. , Physicians and patients alike must recognize it is not necessarily a single disease, but rather a group of varying symptoms, comprising a “heterogeneous” mixture of dysregulatory syndromes. As this goes to press, the new 1994 criteria has just been released. In it (figure 3), CFS is defined by “the presence of the following: 1) clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social or personal activities; and 2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain without joint swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep; and post exertion malaise lasting more than 24 hours.”

There remains to this day no single diagnostic blood test (or other test) to prove this diagnosis. One is left excluding other reasonable medical probabilities, and without recovery over at least a six month period. Newer reports at the AACFS/NIH (American Association for Chronic Fatigue Syndrome/National Institute of Health) conference in Ft. Lauderdale, Oct. 1994, are showing that as little as one month of abnormal fatigue or prolonged illness may be

significant and suspicious. In this author's opinion, what initially appears to be a confusing mixture of symptoms, is understandable, when explained in terms of an immune-dysregulatory /CNS-dysfunctional state. One must remain open to a variety of possible causes or etiologies, perhaps expressed via common "end" pathways in the body. For example, a patient who may present as psychological or create physician "skepticism," may be understood physiologically when analyzed in the context of an dysfunctional/dysregulatory state. Specifically, one means an immune system that, for whatever reason(s), is not returning the body to its normal homeostasis. Fortunately, as more physicians have become familiar with this syndrome, one sees that in spite of its unique qualities, CFS/CFIDS has much in common with other immune-related diseases. Likewise, Psychiatrists and Psychologists are beginning to recognize the complex neuro-physiologic component in what has been labeled "psychological/mental" dysfunction before. (Note: There is and will likely always be a "blurring" of "psychologic" vs. "physiologic" dysfunction in medicine). Rather than the negative connotations of the past, the interconnections and their further understanding should help patients from whichever side of the spectrum they originate.

A correct diagnosis by the primary care physician is unlikely without knowledge of and familiarity with CFS. In the absence of a single, definitive diagnostic tool (figure 4), the physician must always investigate the possibility of an underlying disease. Routine laboratory studies, including a complete blood count, sedimentation rate, urinalysis, basic chemistry panel (electrolytes, kidney and liver function), thyroid screen (TSH and T4), autoimmune disease screen (pursue further if indicated), and tests of muscle enzymes (if indicated) should be performed to rule out other possible/probable causes of fatigue. Patient history and a physical exam may indicate that further studies are needed, such as sinus and chest x-rays, pulmonary function tests, CT or MRI of the head, allergy skin tests, B 12 levels or other metabolic markers, urine studies for heavy metals, cardiac evaluation, or further neurologic testing. It is very important for the physician to choose tests that eliminate "probable" or "likely" derlying causes of CFS/CFIDS, while striving to limit tests in number and expense based on a logical evaluation of the signs and symptoms presented by the patient.

The "consensus definition" of CFS developed by Holmes et al.(figure2) in 1988 represented information gathered by investigators directly from their own practices, as well as field research on the initial outbreaks of this disease. But this has been in dispute and in need of revision since its publication. As noted above, the new 1994 "revision" has just been published. It has been the opinion of this author, and others, that there was potential bias on the part of the researchers using the 1988 definition, as perhaps as many as 50% or more of these cases cannot be traced to an acute, epidemic out-break (this has been corrected in the new edition). The CDC's definition was set up to initiate a basis of scientific research, but it automatically overlooked all the people who have had this syndrome for less than six months (although fatigue may be the problem, it is acknowledged by many that symptoms beyond one month, may be an abnormal state). It ignored the possibility that some sufferers may continue to function in spite of the debilitating symptoms they may be experiencing (perhaps more

common in those one might define as gradual or insidious onset, mildly immune dysregulatory, etc. . . acknowledge by dropping of a specific amount of disability in the new version). And it excluded most children, who seem to have different patterns, varying with age ranges and immune system maturity (still a problem with the 1994 revision). In fact, children generally start off healthier and with more physical reserve than adults, a factor that may logically explain some of the clinical variations we see in these younger patients and even among adults themselves. In referring to the 1988 CDC criteria, many authors often overlook the essential “preamble”. The CDC itself acknowledged that “this definition is intended to serve as the basis for epidemiologic and clinical studies of the Chronic Fatigue Syndrome.” Although it may be a useful guide for the evaluation of a patient with a suggestive illness, the definition remains sufficiently non-specific that it cannot confirm or deny the diagnosis of Chronic Fatigue Syndrome in an individual patient. Chronic Fatigue Syndrome remains a diagnosis of exclusion, and physicians must continue to maintain a high level of suspicion throughout the course of the illness for the possibility that other more occult conditions may be causing the symptoms. We will continue to search in vain for many occult conditions until we are able to define and characterize this phenomenon further.

Fortunately, at the recent AACFS Conference in Ft. Lauderdale, FL., many peer reviewed surveys showed that the “strict” 1988 CDC guideline might truly be only “the tip of an iceberg,” and noted many similarities between patients with fatigue or other immune dysfunctional/dysregulatory/auto-immune illnesses, and those defined as “CFS” by the CDC criteria. The new revision may be much more practical overall, but there will likely still be controversies and debate.

EPIDEMIOLOGY:

The above definitions, flawed or otherwise, have helped lend credibility to the concept of Chronic Fatigue Syndrome. Its limitations and subsequent study design faults have resulted in an acknowledged under-reporting of its incidence in our society. In fact, it is likely that an underestimation of the significance of the illness and dysfunction caused by this syndrome has been occurring all along. The definition implies such a heterogeneous group of patients, that refinements are clearly necessary to distinguish potential sub-groups for further evaluation and study, as well as treatment protocols. It is unlikely that any study of treatments or treatment protocols for “CFS/CFIDS” patients will yield “statistically valid” results without first defining more pointedly the population we intend to study. This factor of heterogeneity probably explains many of the conflicting results in the published studies of this syndrome to date.

This “epi-phenomena” has gone by different names, in different outbreaks dating back to the 1500s. Many authors, have published books and articles that consider the interlinking of various “outbreaks.” The most recent occurrence of groupings probably started some time in the early 1980s in New Zealand (figure 1). In 1984, what was called the “NK syndrome” was defined in Japan. Many physicians recall the major medical announcements at that time. It was believed that researchers in Japan had detected a “new” syndrome with no known viral or

bacterial cause. The primary characteristic present was low NK cells, along with a general dullness of the patients, with loss of interest in both physical and mental activities. Subsequently, epidemics of CFS/CFIDS/Myalgic Encephalomyelitis were reported in Australia and New Zealand. An outbreak in Lake Tahoe fostered recognition of CFIDS in the United States, followed by outbreaks in Philadelphia, Canada, England and Lyndonville, New York, among others. This world-wide phenomenon seems to be continuing, rather than subsiding as in the past.

As a clinician, I have witnessed this phenomenon evolve within my own office practice. Prior to 1988, I was not familiar with the terms Chronic Fatigue Syndrome, CFIDS, or any such names. I recognized the presence of an illness pattern, appearing in my pediatric patients and/or their families in varying numbers that was unpredictable from past experience. The symptoms affected my spouse, as well as parents and children within my practice. The recognized epidemics are significant as they have raised the question of whether specific triggering agent(s) may exist in any given group of similarly affected patients. However, as noted, large numbers of patients have developed this illness independent of any epidemic and without a specific recognizable triggering agent or cause. Many patients seem to have a long-term insidious onset, which may finally lead to an acute exacerbation or flare-up. However, other patients report that they were totally well before an acute, often flu-like illness, from which they could not recover, suddenly overtook them. At the recent AACFS conference in Ft. Lauderdale, it was noted that we may be looking at different morbidity patterns and different clinical patterns/courses between "acute" vs. "chronic" onset patients. Prognosis and long term outcome may differ between these two groups, emphasizing further the need to better define this "heterogeneous" mixture we call CFS/CFIDS.

We have been perhaps the last "academic" country in the world to finally accept the existence of this syndrome. The amount of suffering and morbidity associated with this syndrome is probably enormous. Newsweek, back in 1990, quoted estimates of at least five to ten million people in the U.S. affected by this disorder, with an estimated one million in Los Angeles alone. Researchers familiar with this syndrome quote a possible clinical occurrence rate at 3% - 5% of our population (or higher !). Currently epidemiologists are finding incidents of 1 - 1.5%, acknowledging probable under-reporting. We urgently need to implement a "controlled" database and research tools to help define and control this disorder as rapidly as possible.

ETIOLOGY:

There are many reports, particularly in the British literature, suggesting a connection to the coxsackie/enteroviruses. While in the USA it has been suggested that many cases may be linked to the Herpes family of viruses (i.e., EBV, HHV6, HHV7, CMV, etc.), , , , Neither theory has been conclusively proven, nor has any contagability been demonstrated, although some have inferred it based upon the incidents of epidemic outbreaks. If an infectious etiology indeed exists, it may be as ordinary as the common cold, or so rare that we have not yet developed the tools to either identify or study it. Based on my twelve years of office

observation and clinical experience, if there is indeed a period of contagability, this author doubts that it occurs during the chronic state, or even during the “acute” period, after 2 weeks to 2 months, if at all. Having once been triggered by an illness, agent, trauma, combination of stresses, etc., irrespective of any underlying cause, it is the inability of the immune system and/or CNS (Central Nervous System) to return to a normal homeostasis that probably best explains the clinical duration and variability of this syndrome. Whether any agent remains or is ongoing is subject to clinical speculation. This author tends to believe there will be some patients in which a background virus, retro-virus, or “stealth” virus may play a role, but there are likely to be many patients in an immune dysfunction/dysregulatory state in which no specific agent (or factor) continues to affect the patient.

What does seem likely is that we are confronted with an illness that has multiple etiologies, multiple origins, and various clinical manifestations. Genetic predisposition to this syndrome may have a great deal to do with why certain individuals suffer these symptoms. What we recognize to be heterogeneous expressions may be linked, or even treatable, via the common pathway of an immune dysregulatory / CNS dysfunctional state. Outbreaks of this syndrome have been observed as occurring in clusters larger than those reasonably explained as chance, therefore compatible with the notion of a transmissible etiology. Current research suggests the probability of a retro-viral like agent, or another new, unknown virus, that possibly predisposes (or acts in “predisposed” individuals) some people to this syndrome, and/or simultaneously functioning as part of the ongoing illness in others? An alarmingly rapid and sustained increase in cases over the last ten to twelve years strongly infers a common environmental cause or possible co-factor. Perhaps the decreased protection of the ozone layer is creating new viral mutations and/or a generally altered immune state. The concept of a world-wide onslaught of immune compromised/dysregulatory state is quite plausible, as evidenced by multiple incidents affecting humans as well as other species that have been reported over the last decade.

Theories that this could be a primary psycho neurosis are defeated by several factors: the similarity in the patients’ descriptions of their illness, the increased clinical associations of signs and symptoms as a group consistent only with this type of illness, and in “acute” onset patients, the similarity in how their symptoms first appeared. Patients, particularly adults, tend to give similar descriptions of the onset of their illness. A majority of these patients express the suddenness with which they were overtaken by the symptoms, having felt perfectly healthy before then. However, it should be noted that sudden onset does not seem to be the most common initial presentation in children. This “previous state of wellness” should be scrutinized with a detailed medical history. The concept of “well” may be a particularly difficult term to apply to children, who may lack prospective as to what is normal. In fact, as noted above, upon further investigation, a large number of adults, adolescents, and children report recurrent minor illness, a childhood history of significant allergies, particularly to food or obvious environmental factors and/or a degree of fatigue or “laziness” when compared to their friends or siblings. None-the-less, in what might be termed the more acute onset or “activation”

patients often remember the exact day they developed a simple “cold” or “flu”, accompanied by a sore throat, cervical adenopathy, myalgia, fever, recurrent gastrointestinal symptoms and profound fatigue which then developed into this syndrome.

By now a predictable pattern has emerged within my own practice, and that of others. This pattern includes increased allergies, ear infections, pharyngitis, bronchitis, and recurrent minor illnesses. In this author’s opinion, the agent that triggers this in acute cases may be infectious, but is probably one of thirty or forty different agents. Some people who are predisposed to this syndrome may go into a CFIDS like state, while many people may be adversely affected by exposure to a particular agent for a finite period of time, usually a few weeks, then return to “normal”.

It seems probable that this disease has an element of genetic predisposition (confirmed in emerging epidemiologic studies). In following a number of families in my practice, not all members of the same family become ill. Often one child and/or one parent alone is affected. This likely implies a lack of ongoing contagion, if any, associated with this syndrome, suggesting genetic predisposition with probable multiple triggering agents or events. These can include viruses, stress, various traumas, etc., setting off a state in the body in which the immune system, the CNS, or both, do not come back to a normal functioning level.

What is the origin of this illness? We may find thirty or forty different factors can be involved. This writer wonders if CFIDS is not an actual virus, but rather an altered response to a changing environment or agents, which are probably acting as cofactors. Are we reacting to ozone layer depletion? Is there some other environmental condition creating or bringing out a genetic disposition for this phenomenon in an increasing percentage of the population? There certainly appears to be reason for great concern. Why are we experiencing such high levels of this syndrome? Why did we start with an epidemic some time in the late ‘70s, early ‘80s that, unlike past epidemics, has never stopped?

PRESENTATION IN CHILDREN:

At an International Conference on PVFS (Post Viral Fatigue Syndrome, before name change) years ago, Dr. Byron Hyde from Ottawa, Canada, identified this syndrome as an overlooked epidemic in children. He noted that children generally have been excluded from documented studies. Dr. Hyde said, “It is evident we are not recognizing these children: they are there. They are there in large numbers. Depression, loss of energy, retardation of thought process, impairment of concentration, etc. These may be dyslexics, children that were getting good marks in grades six and seven, come down with a minor viral infection, and then become school problems. They sometimes get kicked out of school, sometimes sent off to psychologists. Parents do not believe these kids, the doctors definitely don’t. Frequently physicians may start blaming the parents for harassing or injuring the child in some way. Impairment of memory, disorders of sleep, the behavioral disorders are typical of the changes

you see in children.” The current rise in attention to Munchausen Syndrome or Munchausen Syndrome by proxy in the Pediatric literature lends credibility to Dr. Hyde’s worst fears. How many of these parents are being falsely accused? How many of the children themselves are labeled as malingerers or hypochondriacs? One can only wonder with dread how many suffering from a very real physiologic dysfunction are not receiving any treatment or support from their families or the medical community.

Any parent, physician, educator, or counselor should be suspicious about the previously active child who has lately become a couch potato (figure 5). It is often a child who has recurrent illnesses, sinusitis, ear infections, bronchitis, and who does not feel well on weekends, as well as school days. These children will complain every day and lose the time they should be devoting to valuable play activities. Frequently in my practice a parent does not recognize a decrease in play stamina, but rather the increase after treatment. In retrospect, it seems evident that these children were not functioning at their full potential, but it is a very difficult judgment to make in children. How can the average parent know what is their child’s “full” potential?

Cognitive problems may be a primary symptom of CFS, particularly in children. Affected children frequently experience difficulties in the school environment. They are typically unable to concentrate and demonstrate lack of memory skills. A common presentation is a child who is able to read a book, but cannot recall what was read, or a child who cannot remember what was said immediately after the teacher has delivered a lesson. One can appreciate what this has done to a child’s self-image when applying the descriptions of this syndrome we have heard from its adult victims. Imagine a child who knows he is doing poorly in school, but has no basis for understanding why. It is a very frustrating situation because CFS/CFIDS children truly want to succeed. They want to go out and play and do all of the things they see their peers doing. Eventually, they lose hope in doing well and may even become behavior problems. As Dr. Hyde has noted, they become difficult kids and may eventually turn to drugs, and even suicide (Perhaps we will come to learn that this syndrome partly underlies the increased adolescent drug use and suicide we are experiencing today). If their physiologic dysfunction remains undetected and untreated, it is unlikely counseling or therapy alone will be very successful. One must always be suspicious regarding any change in physical or behavioral patterns that fall outside the range of what we accept as “normal”. These children tend to be very anxious and clinging. They typically have poor self-esteem and have an understandable reluctance to attend school as a result of the constant failure they have suffered there. These children will often adopt an attitude of lassitude as a facade. They frequently have a disturbed sleep pattern and experience nightmares, restless sleep, and/or a “non-restorative” sleep. Sometimes a change in body weight is observed. They have, in the past, been diagnosed as depressed, lazy, or under-achievers. Often parental “over-involvement” has been blamed. As noted above, how many of the cases being referred to in the Pediatric literature as Munchausen Syndrome (or Munchausen Syndrome by proxy), may truly be undiagnosed or unrecognized CFS/CFIDS?

A medical history may suggest signs of cognitive dysfunction, particularly lack of focus, inability to concentrate on school work, perhaps the label of “quiet” ADD/ADHD (Attention Deficit Disorder). Almost all recent academic pediatric articles have focused on the high incidence of school dysfunction, school absenteeism, and need for home tutoring; often defining these problems as secondary to the physical dysfunction, rather than arising from a primary cognitive dysfunction. Fortunately, the majority of recent articles, while they do not understand this phenomenon in children, have generally noted the probable legitimacy of many of the patients followed, and ruled out other diagnoses (including psychological) over time. It is worth noting that over time, very few of these patients go on to “another” diagnosis or explanation.

A past history of allergies might actually be an indication of the early dysfunctional stages of CFS (as discussed here in terms of an immune dysregulatory state/epiphenomenon), or at least a reason for increased suspicion. Allergic patients often experience decreased host defenses to an infectious agent, with increased immunologic responsiveness, which is sometimes genetically rooted. Because allergic patients have T-cell abnormalities, an inference can be made that a propensity toward immune dysfunction may be involved with the pathogenesis of CFS. CFS/CFIDS is quite possibly linked to “The Allergic-Fatigue Syndrome” that is currently ascribed to environmental agents or factors. The concept of a common expression of an immune dysregulatory / CNS dysfunctional state may promote greater understanding of this strange epiphenomenon called CFIDS. It certainly seems to be the only logical interpretation available to us given our current information. When viewed in this context, CFIDS’ multiplicity of symptoms a clinical progression can be put into a logical pattern. Perhaps it will overlap to many “idiopathic” or “auto-immune” processes discussed in the medical literature of today, linking many otherwise conflicting reports.

Rheumatoid symptoms may also be significant in the history of the CFIDS sufferer. Not the typical “growing” pains, but limb/joint pains not classifiable into any of the established or typical Rheumatoid patterns. This is especially significant when these symptoms are present following a known viral URI (Upper Respiratory Infection), flu, or mono-like illness.

In diagnosing children with various expressions of this syndrome, fatigue may not be the primary complaint. Children in general have much more physical reserve than adults. There may be no obvious physical limitation, or often, one that may become obvious only when the child improves with therapy. This is a very key issue to understanding this syndrome, especially in children. If looked upon as a stressful state or ongoing immune/metabolic dysfunction, there will be different expressions of this stress and in general, children will tolerate the “physical” manifestations better than adults. Normal, healthy children are generally active. They want to be active and they have lots of the necessary energy. One characteristic of the differentiation of this syndrome in children versus adults is that the affected adult usually has a very clear lack of energy. The child who may be a little slower, a little less active, but still almost always has sufficient reserve to keep up with their peers, because, on the average, their younger bodies may be viewed as healthier than their adult counterparts. In fact as

severity increases and a child or adolescent cannot keep up with their peers, maintain normal attendance at school, etc., there may be secondary esteem and ego issues compounding the situation.

Apart from the intellectual dysfunction caused by CFIDS, sleep disturbance appears to be a major indicator. Common complaints are very restless sleep, absence of dreams or strange dreams, and awakening tired. One can sleep 6, 8, 10, or even 12 hours yet awaken feeling tired due to what is called "non-restorative" sleep. Researchers have shown that patients with Chronic Fatigue Syndrome do not go into a normal stage IV or REM sleep cycle. Such a patient will experience difficulty in forming memories and in other "restorative functions" due to this loss.

It is critical that we learn to define and recognize this phenomenon in children. In spite of my familiarity with this illness, even I thought Dr. Hyde must have been exaggerating when I first heard him speak on this subject. Initially, I found some of his conclusions almost "far-fetched". But, as time has passed, it has become obvious that Dr. Hyde was not overstating the case in the slightest. The potential cost to children suffering from this dysfunction is staggering, and is quite likely the culprit underlying many scholastic problems and social failures.

PHYSICAL EXAM:

Physical examination may reveal no obvious or remarkable evidence of classical illness. A common presentation is recurrent swollen lymph nodes with or without a low-grade temperature elevation or depression. Patients may have abdominal pain, muscular or skeletal pain or discomfort, and/or tender points such as that associated with fibromyalgia (it remains this author's opinion that fibromyalgia and CFIDS are disorders reflecting varying clinical expressions of similar or even the same epiphenomena). An abnormal oropharyngeal exam is quite typical, frequently described as a "red crescent". Lately there is increased reporting of dental gingival disease, likely representing a chronic, low-grade, gingivitis, stomatitis in many of the more chronic patients. Oral thrush can be a marker for Candida in some of the patients. One may observe frequent incidences of atypical rashes. There may be occasional balance problems, and patients may exhibit fine motor signs or "soft" neurological signs. Usually no significant neuro-muscular pathology is uncovered by standard exams.

There may be signs of recurrent allergies (boggy nasal turbinates, nasal mucosal redness, "allergic shiners," etc.) or mild/moderate bronchospasm, restrictive airway disease. This airway dysfunction may be secondary to recurrent infections or secondary to reactive airway disease.

LABORATORY:

Elevated antibody titers to EBV, CMV, Herpes VI or VII, and abnormal lymphocyte surface markers for T cells, B cells, and NK cells are frequent findings in CFS patients. Immunoglobulins and IgG subclasses are abnormal in 40% to 70% of patients. Also,

antibodies to a retro-virus have been reported in 41% of CFS patients compared with 6% of healthy controls in one study. The “contribution” of a retro-virus is disputed by other authors, and remains an area for technology and appropriate studies to further define. If one observes an elevated titer of antibody to a particular virus (or retro-virus) at the time of diagnosis of CFS, it is not possible to identify which factor appeared first nor which of the two, if either, might play a causal role. The scattering of reports and lab results has contributed to the confusion surrounding this syndrome. If examined within the context of an immune-dysregulatory state, with potentially varying degrees of expression and different possible origins in various patient cohorts, one can begin to make sense of these different reports. It seems more and more likely that we will be able to understand these variables only under the auspices of a controlled database.

In articles about adults, one finds reports of low and/or elevated natural killer cell activity., There may be a change in T-4/T-8 ratio. Patients may exhibit activated/abnormal T-cell subsets, abnormal immunoglobulin levels, IgG subclass abnormalities, altered Interleukin-2 activity (generally assuming an elevated Interleukin 2 soluble receptor), and various other interleukin/cytokine abnormalities which have been reported. There may or may not be elevated alpha-interferon levels, plus or minus elevated rogi cell assays, possibly a weakly positive ANA. There have been reports of a decrease or anergy in skin testing for delayed hypersensitivity (the part of the immune system responsible for dealing with fungi and similar pathogens). Atopy (“hypersensitivity “ due to hereditary influence) may be a predisposing factor, as it appears to be present in up to 80% of patients with CFS. The salient feature that is repeatedly seen throughout this process is that of a dysfunctional/dysregulated system, operating with various degrees of activation or impaired reception, or inactivation with decreased function. The wide range of results may be explained by the changing status of the patient and at which stage of the disease process they are tested. Work is underway by Dr. Nancy Klimas, to define “patterns” of cytokine abnormalities, as a means to further define and understand various patient groups.

Immunologic findings in children generally seem to be similar to those found in adults. However, there remains significantly less clinical experience with children in grouping of immune patterns. The physician may observe low natural killer cells and low Immunoglobulins (particularly IgG, IgG subclasses, and/or IgA). As noted, various viral titers have shown mixed results. Testing may show activation or inactivation of the immune system (figure 4): It has been this author’s observation to find some patients with elevated IgM (a possible marker of viral/immune activation) or elevated IgE (perhaps reflective in some patients of increased allergies).

Routine lab tests on adults and children vary. Looking at routine lab tests in children and adults, one may show elevated Cholesterol, a sign of mitochondrial dysfunction, mildly elevated liver functions, a possible indication of viral irritation, inflammation, or other liver dysfunction. Abnormal elevated TSH or low T4, reflecting thyroid dysfunction (often assumed to be present clinically but difficult to measure peripherally), and/or thyroid antibodies, a sign of auto-immune thyroiditis, may be seen. Overall, one looks for “soft” signs of metabolic dysfunction, but we still lack a diagnostic or classical pattern to define

a patient with this illness. There have been reports of abnormal viral DNA particles identifiable by PCR probe technique and abnormal muscle biopsies,, , although these are somewhat limited tools surrounded by controversy.

Today, the existence of CFS/CFIDS appears best supported objectively by evidence of abnormal NeuroSPECT scans in sufferers, (author's work with children, pending publication). Pathways with decreased blood flow apparently have decreased function. A study by Dr. Jay Goldstein and Dr. Ismael Mena, has shown, using a controlled population of normal adults and adults with CFIDS, that they are clearly not the same as adults with depression. CFIDS is not depression, although patients with CFIDS can obviously have a reason to be depressed, and may have some overlap of areas on NeuroSPECT. There is a quantifiable, statistically significant difference that is physiologic, not psychologic, in origin.

As noted, findings on NeuroSPECT scans help to confirm dysfunction and show that a patient's CNS/brain is not functioning properly. What is very promising is that the results can be altered with intervention. So far, most brain malfunction seems to be reactive, and the SPECT scans improve when the body becomes healthier. None-the-less, there is preliminary evidence that permanent damage may result from prolonged malfunctioning, confirming this author's belief that this is not a benign process. There is a potentially significant loss to adults and children who are afflicted by this disease that only an accelerated research effort can mitigate.

Fortunately, an increasing number of psychologists and psychiatrists now recognize that CFS/CFIDS does not have a psychological origin as it does not reflect the typical presentations of classic fatigue or depression, confirming the likelihood of an organic basis for the disease. Additionally, children are less frequently known to present with psycho-somatic illness than are adults.

It is this author's opinion, that unless one wished to hypothesize a "mass hysteria or psychosis", the similarity of presentation in many patients cannot be conceived as psychologic in onset. This is being supported by research projects (works in process, presentations at the Ft. Lauderdale, AACFS conference) confirming the differences between patients with CFIDS, normals, patients with major depression, and some patients with other immune related illnesses.

DOES CANDIDA PLAY A ROLE?

The relationship between CFS/CFIDS and Candida, or other yeast, is not yet understood in the medical community. There is no standardized test to date for verifying or confirming the notion of a yeast overgrowth and its potential adverse side-effects. As with CFIDS itself, the general medical approach to this area has been a reluctance to consider any possible explanations that cannot be measured. While it has yet to be proven, it seems none-the-less logical to this author that the presence of Candida or other opportunistic organisms in CFIDS patients, while not likely the cause, may certainly contribute to the dysfunction experienced by the patient. Yeast-like breath or a

distinct sour milk breath smell may be a clue in a child or adult that a yeast over-growth has occurred. While it has been correctly argued that yeast is abnormal G I pathogen in most humans, this author strongly suspects that Candida/yeast may take the form of a pathogenic overgrowth in a patient who is in an immune dysrulatory state, specifically in the case of CFIDS.

As noted, there have been numerous reports of decreases in delayed-hypersensitivity in CFIDS adult patients. Significantly, this is the part of the immune system responsible for controlling yeast and other such pathogens. Assuming then, that Candida may be a part of the CFIDS syndrome in some patients, it is most likely a secondary opportunistic infection and not a primary cause of illness. It is very doubtful that a patient with CFIDS is compromised enough to allow disseminated fungal conditions. Instead, in some cases, one may observe a G I or chronic vaginal overgrowth. The GI overgrowth could potentially interfere with a patients normal flora, GI function, and absorption of nutrients; and/or as some researchers hypothesize, there may be a release of toxic metabolic products, with direct effect on a patients CNS. The later theories are receiving some support by the early reports of abnormal metabolic products in the urine of CFS/CFIDS patients. Regardless of the theory, treating Candida often does seem helpful in returning the body to a normal state. Final answers will await appropriately controlled studies, and the techniques and measurements to perform them.

POSSIBLE THERAPIES:

At this point in time any discussion of therapies must be deemed antedotal. Currently, there are no agents that have shown success consistently in trials. None-the-less, there is an emerging base of clinical experience that can serve as a rational approach to therapy as we await more definitive conclusions. Ultimately, depending on evolving physiology and ultimate etiologies, we will one day likely have various immune-modulators at our disposal. Possibly they will include direct anti-viral agents or other specific agents to use as therapy for this condition. Progress will only occur in the context of a clinical database and controlled trials using defined patients. The rapid establishment of a clinically- oriented database is critical to enable true evaluation of therapeutic agents. It is important to note that the discrepancies among patient samples will likely be resolved and understood only as we develop tools to define similarities or common patterns within this heterogeneous syndrome. Build in upon principles applied recently in approaching HIV and other illness, an essential goal must be to inspire clinical cooperation among health professionals. By working together via a clinical, inter-relational database, it should be possible to accelerate the development of methods or patterns for identification and separation of patient groups. This will be made possible the application of “controlled” therapy trials for the benefit of sufferers of this syndrome/epiphenomena.

In taking a therapeutic approach, the physician should start with the easily identifiable issues and proceed further as indicated. It is logical to deal with the areas of dysfunction in which we are experienced and then “see what is left over”. This author would emphasize the need for

treating the overall “well-being” of a patient, rather than just the symptoms. My experiences have guided me to formulate a treatment approach wherein I address whatever dysfunction(s) I possibly can. The goal is to maintain maximum function until the body, with or without medication, can return to normal.

When one or more family members are affected with this syndrome, it is a primary requisite that they receive understanding and support from the rest of the family system. As noted previously, the medical system’s resistance to respond to this condition, through lack of understanding, has caused untold amounts of family problems. This is especially stinging when the strife results from the incorrect advice of the primary health care-giver or a specialist who lacks knowledge about this syndrome. This author has seen repeated examples of children and adults who have shown dramatic improvement with the recognition of their condition and some “supportive” therapy, both medical and social.

SUPPORTIVE THERAPY:

Under the modalities of what might be called “supportive” therapy, we have antibacterials, antifungals, antivirals, antidepressants, antihistamines, anti-inflammatories, vitamins, minerals, and other “nutritional” supplements. Any or all of these may aid the effort to bring about a return to normal functioning. The concept of trying to “normalize” and improve body functioning in an orderly, logical manner, has served this author well over the years. While specific/directed modes of therapy are on the near horizon, many patients can be helped while awaiting ultimate answers. In many cases, children and adults have become “well” as their immune system was able to “stabilize” itself, after some “help”. It remains this author’s overall optimism that successful therapy is currently possible, and can become simpler and likely more specific in the near future.

It appears very likely that allergies have a major effect on adults and children with CFS symptoms. Patients frequently present with a history of allergies and/or recent allergy exacerbation’s as part of their symptomatology. My experience and that of many other physicians suggests that vigorous effort be made in the direction of supportive therapies involving allergies. The less the body’s immune system is triggered negatively, the easier it may be to return to a state of normalcy or balance. Elimination diets have served as a major role in therapies used in my practice over the years. A patient with a turned-on, dysregulated immune system may be sensitive to any number of environmental or nutritional antigens. While one cannot always control a sufferer’s environment, we can exercise control over foods ingested. Immediate and intense attention to eliminating food irritants cannot be stressed too much. In tandem, I recommend the aggressive use of low-dose, overnight antihistamines (to control PND - st Nasal Drip), and inhaled nasal or bronchial sprays when indicated. By using this course of action, one can frequently minimize recurrent episodes of sinusitis, otitis, bronchitis that frequently plague these patients. Antihistamines used thus become allergy mediators. Taking a low-dose antihistamine at bedtime will often stop postnasal drip. If postnasal drip can be stopped, and/or other sources of congestion controlled,

sinus and ear infections and their symptomatic headaches may be reduced. It has been my experience that much of the shortness of breath patients experience can be controlled by judicious allergy avoidance and appropriate bronchial sprays, and by treating secondary bronchitis/infections when indicated.

Antidepressants, particularly Prozac, Zoloft, Paxil, and Wellbutrin, have been used for a number of years by clinicians working with CFIDS patients. Antidepressants can and do play a role, but not because people afflicted with this are depressed or “depression” in origin as has been so often falsely assumed. At low doses, Prozac, Zoloft, Paxil, and very possibly Wellbutrin or BuSpar work on those areas of the brain that are decreased in function as shown by NeuroSPECT scan (clinical reports). Contrary to those physicians who have tried to imply that their use indicates that CFIDS is a depressive disorder, we actually find that most patients were normal (or high functioning) adults and/or children prior to the onslaught of their illness. Certainly, as acknowledged by even the CDC and NIH over the last few years, and confirmed by reports looking at different “populations” of patients, patients have a basis for developing depression as a result of this illness. As long as the depression is not “preexisti” (open to interpretation), it is not very likely the cause of the illness. Nor does its presence exclude a patient from the new CDC definition.

While many physicians have used Sinequan (Doxepin hydrochloride), Desyrel (Trazodone HCL), Tofranil (Imipramine HCL), Elavil (Amitriptyline HCl), etc. to induce sleep at night with various degrees of success, there were clinical reports years ago about “success” using low dosages of Prozac in the morning to help sleep problems. Prozac, Zoloft, and Paxil may help to stabilize/normalize a part of the central nervous system dysfunction associated with this illness. Prozac has been demonstrated to actually increase blood flow in areas that have been noted to be under-perfused on NeuroSPECT scans. While not widely publicized, Prozac was reported to be an immune-modulator at low dosages in its early days of use. When I learned of this several years ago, I became much more comfortable about prescribing Prozac, both with children and adults, since it appears to have a directly beneficial effect, and does not imply “medicate” the symptom. Addressing the issue of sleep dysfunction and, to some degree, cognitive dysfunction, suggests the use of these agents as first choices in adults and, increasingly, in children. While I do not regard these medications as a cure, they may be a useful tool in helping to restore function to areas of the brain that are dysfunctional. However, these medications, as in all cases, should not be used if any negative effects are noted. As this is a long-term condition, the clinician must avoid any agent that creates negative or potentially negative effects. An individual should not stay on a medication that does not agree with them, choosing to avoid such agents, particularly in children. Long-term safety and side effects must always be of concern.

Interestingly, consistent with the above approach and clinical experience, there were a few reports at the recent AACFS conference showing that a patient being on a tricyclic type of antidepressant showed no change on the

“physiologic” parameters being evaluated. As part of this overall approach, this author

cannot over stress the idea of trying to help “normalize” function, not just put a “band-aid” on the symptoms.

My experience has shown that afflicted patients can avoid some of the typical “down time” if secondary infections are treated as early as possible. Swollen glands, redness, and pain in the throat should not be accepted as just part of the CFIDS profile. I consider any antibacterial or antiviral therapies to fall under the heading of supportive therapies at present. If the body is trying to fight an infection with a compromised/dysregulated immune system, clearly it needs the help of supportive resources. Antibiotics are indicated to help fight recurrent sinusitis, pharyngitis, bronchitis, etc. Antibiotics should always be used judiciously, choosing the most specific medication that will work. Frequently, based on findings or blood count, a course of Erythromycin (a unique, bacteriostatic medication, it “paralyzes” the function of many organisms, but the body must finish off the “killing”, thus being less disruptive to the body's normal flora/organisms), or perhaps a heavier antibiotic, can help reverse these “low” periods. It has been my experience, that many “flare-ups” of this syndrome seem traceable to the stress of an infection, and there has been a notable improved recovery for patients who are treated for this “stress”. Often when I see a red throat, cervical adenopathy (frequent flare-ups in patients), I turn to the use of Erythromycin with good success. With a lack of controlled studies, one must individualize treatment to each patient. However, in all cases the physician should respond rapidly to secondary flare-ups and discourage the patient from accepting them as unavoidable or untreatable.

Likewise, antivirals have their place as “supportive” therapy. Depending upon blood count, viral titers, clinical symptoms, etc., there may be applications for Zovirax, Amantadine, Flumadine, and others. As always, clinical judgment, safety, and individualization are essential. There are multiple anecdotal stories of agents helping, and there are times when these agents seem to be very helpful. Again, subject to conflicting reports about various treatments, we will one day be able to define this “heterogeneous” epiphenomena we call CFS/CFIDS, and thus evaluate under which circumstance or within which group of patients an agent may be helpful. Without this “subdivision” of patients, most therapies are likely to remain confusing and of questionable significance, even if very helpful within a sub-group of this disorder.

Under the category of symptomatic therapies are nonsteroidal anti-inflammatories and other analgesics. Physicians have prescribed these agents for the last 20-30 years to treat muscle pains, body aches, joint and bone discomfort. They are still used to routinely treat patients with rheumatoid diseases, symptomatically, not “long-term” curatively. To this day there remains no “cure” for most of these diseases. On a short-term basis this approach relieves some pain and, certainly in regards to an arthritic process, may help slow down or minimize long term damage. The treatment of the syndrome we call CFIDS demands a common-sense approach to the symptoms and an effort to provide what relief possible. Aches, pains, sore throats, and headaches can be alleviated with anti-inflammatory drugs, milder analgesics, antihistamines, decongestants, antibiotics or anti-virals where indicated. Habit-forming

medications or medications without long term safety should be avoided. On a long-term basis, it is preferable “shut-off” the “negative” process by creating a remission or cure, rather than simply treating the “external”/reactive symptoms.

The effect of exercise is an area of concern for most patients and physicians. When a patient is very ill, exercise does not help; and in fact may be harmful or another “negative”. At the point where one crosses over into an anaerobic metabolism, the effect is probably harmful to the CFS patient, further stressing their systems. We know that patients with CFIDS whose metabolism is “off-balance” suffer ill effects from exerted exercise. My advice generally is if the patient feels worse the day following exercise, such activity should be curtailed or stopped if necessary. Once the patient’s condition shows improvement, moderate, non-aerobic exercise can be reinstituted. Slowly, the patient can rebuild their strength and exercise tolerance, but I believe only as part of an “up-cycle” responding therapeutically.

Nutrition has never been a major emphasis of medical research in this country. Europe, Asia and most other industrialized countries have always been ahead of us in the area of alternative medications. Asia has an ancient history in herbal medicine. Without a specific agent to direct therapy toward, attempting to “re-normalize” the body’s function makes great sense. The frustration is that we need to be open to untraditional treatments, but somehow avoid “scams.” Most sufferers are fatigued to some degree and metabolically dysfunctional. Nutritional support or herbal therapies may be appropriate, but there must be a mechanism of testing for efficacy, or at least absorbability and potential function. Many “nutritional” therapies as marketed are not absorbable, and while appearing in theory to be a good idea, are often useless. Work I did in the mid 1980’s supports the potential usefulness of some of these remedies. Without appropriate clinical trials (a primary reason I pulled away from further research in these fields at the time), patients and doctors have no way to judge potential efficacy, safety, cost effectiveness, etc., of these agents.

Practically, the patient should take care to supply their body with the basic vitamins, minerals and energy sources that it needs. While there are several theories on appropriate diets for CFS patients, I generally stress a diet that is high in protein as a source of amino acids. I recommend that patients consume large portions of chicken, fish, turkey, some red meats and protein-composed vegetables. Protein supplements may be helpful, but remain difficult to evaluate for efficacy and legitimacy at present. My findings from work in the mid 1980’s revealed that many of my CFS/CFIDS patients appeared to have 30% to 50% of their amino acids below normal on a reliable serum electrophoresis type of report. Whether low from lack of absorption or over-utilization (both concepts logical), the body cannot function normally when the amino acids are low, for they are the building blocks of most chemicals and hormones in the body. While some researchers have expressed concern over “stressing” the liver, I have found that mild liver enzyme elevations often improve as a patient’s body became healthier. Providing an adequate quantity of protein and their amino acids remains essential, particularly within an overall treatment plan.

Multiple vitamins may yield some benefit, but I do not believe megavitamin therapy provides long-term help, and in some cases, may be harmful. I have never subscribed to high-dose mega-vitamin or IV supplements for that reason. Their potential harm never seemed outweighed by their potential benefits. Subsequently, while there are antedotal reports of short-term success, vitamin therapy does not appear to have produced any long-term results in a significant number of patients, or in any controlled trials. I do believe a good, high potency multiple vitamin, iron, mineral combination can be helpful. Depending upon lab test results, at times I recommend extra calcium, extra magnesium or extra iron to be indicated along with prescribing extra doses of vitamin C, usually 1000 to 2000 mg. per day. I view using mega-dose vitamin modalities as an effort to "squeeze" some energy out of a depleted body; while, in fact, having done nothing to build up that body or to turn off the dysregulatory process.

While there has been very little in the way of properly controlled trials using nutritional therapies published, Behan et al examined 63 adults in a double-blind placebo study using essential fatty acids. They noted a 74% improvement compared to 23% on placebo. Serum fatty acid levels tend to fall in acute and severe chronic viral infections. These fatty acids may be important in neuronal metabolism, but their effect has not been established in children. Interestingly, at the NIH-sponsored conference in Albany, N.Y., in Oct. 1992, EFA's (Essentially Fatty Acids) were mentioned a number of times antedotally. As always, care must be taken in obtaining products that are pure and of high quality. At the recent AACFS Ft. Lauderdale conference Oct. 1994, some researchers looking at EFA's actually reported an improvement in "normals" compared to patients. This should re-emphasize the need for all of us to further refine and define patient populations, to appropriately judge therapeutic trials. Unfortunately, as noted, there are many products offered to the public with no efficacy and no proof of absorbability or usability. Until we learn more about supplements from future studies, I would caution all patients to follow common sense nutritionally, avoiding any unnecessary and expensive products unless they are proven to be safe and come with a "money-back guarantee" for a reasonable trial period.

Finally, under supportive therapies, one deals with the issue of Candida. While we cannot measure the presence of Candida accurately, we can treat its theoretical effect through a therapeutic trial. If appropriate anti-fungal/Candida therapy is effected and no "kill-off" or die-off (a period of feeling "worse" shortly after starting therapy) is experienced, then yeast is probably not a significant problem for that patient. If, however, a clinical trial shows "kill-off" followed by improvement, continued therapy is warranted. Until better markers or lab tests evolve, there will remain a very high level of controversy regarding Candida or "yeast". Acknowledging the controversy, my first choice of treatment is Nizoral with an increasing preference for Diflucan, were it not for its expense. Generally, if working successfully, I will prescribe Nizoral for at least 5 - 6 months. Patients should be monitored regularly while on this drug for elevations of liver enzymes. Later, I switch to an oral "maintenae" medicine such as Nilstat (often not strong enough) or oral Amphoterecin B. While significantly stronger than Nilstat, Amphoterecin B is very safe when taken orally, but highly toxic as licensed in

this country for IV usage. It is available over the counter in many parts of Europe, and can be obtained by prescription via special “compounding” at College Pharmacy in Denver, Colorado. While one should try to avoid sugars and yeast-containing foods such as breads, rolls, beer, wine, etc., a sensible diet, avoiding the worst offenders, is most practical for a long-term therapy. Severely restrictive diets are too difficult to follow and only represent supportive help in general, not a cure for this disorder. Positive results have been easier to obtain with the combined help of medication, rather than by diet alone.

IMMUNE-MODULATORS:

In this author’s opinion, “Immune Modulators” remain the hope for the immediate future. These are agents that re-regulate and adjust the immune system. It will probably be years before we will have specific treatments to cure CFIDS in those patients in whom specific etiologies may be present. Therefore, for all patients, we need to try to understand and combat the dysregulated immune system in the interim. A dysfunctional/dysregulated immune system responds inappropriately by fighting off an illness or stress that may no longer be there. Such a state produces a variety of symptoms caused by the immune system’s faulty regulation. As noted, research is confirming cytokine abnormalities and the concept of a dysregulated, often inappropriately activated immune system in CFS/CFIDS patients.

As a result of immune system research relating to AIDS/HIV over the last 10 - 12 years, certain agents have been uncovered that may have the potential to help patients with CFIDS, or other immune-modulated disorders. DNA/gene therapy may one day be developed for treatment of CFIDS and other dysregulatory states. But that sort of treatment is the medicine of the future, not the present. For today, immune modulators may provide solutions while we continue to search for specific etiologies and other areas of treatable dysfunction. This author suspects that this approach has the potential to help people with many of the collagen vascular/autoimmune related disorders including lupus, and rheumatoid arthritis among other illnesses. Through an understanding of cytokine profiles or other specific abnormalities, agents can be evaluated in appropriately structured trials that will likely provide much needed help NOW.

Gamma globulin, an agent that has been a part of traditional medical treatment for years, may temporarily help some patients. Gamma globulin’s effectiveness is as an immune modulator. Since it does not in general seem curative or even universally successful, I do not generally agree with prescribing IV gamma globulin for CFIDS, as do some other physicians. There are limited and inconsistent reports of patient response and it is extremely costly. There are dangers of severe “reactions” to this product and a possible transmission of Hepatitis C (low probability). None-the-less, it may improve the level at which some patients function at times, but at a very questionable “cost vs. gain” comparison. IM gamma globulin, which is given by an injection, is relatively inexpensive, safer than the type administered by IV, and may have

similar benefits in some patients. It has been this author's experience that as many as 50-60% of patients may benefit by its use when they are in a "down" condition. When the illness has exacerbated and the sufferer is feeling especially weak and tired, a shot of gamma globulin can yield some relief. If helpful, it may be repeated at intervals from 1 to 4 weeks for a short period of time. For those who do respond, repeated injections of gamma globulin are safe, but should be used judiciously. Unfortunately, between 40 to 50% of patients seem to experience no improvement from gamma globulin, and in those cases, continued use would seem futile.

Kutapressin is a mixture of agents prepared from pig liver. Dr's Steinbeck and Hermann defined this mixture in the early 1980's as about 20-25% "immune active". Kutapressin has been used for the last 40 years as therapy for a wide variety of dermatologic conditions. Favorable response to administration of Kutapressin in patients with acne vulgaris, Herpes Zoster, Poison Ivy Dermatitis, Pityriasis Rosea, Seborrheic Dermatitis, Urticaria, Eczema, Severe Sunburn, and Rosacea has been reported in the past. Kutapressin has seemed very helpful (antedotally) in my practice and that of others when used as an immune modulator in treating CFIDS.

In a number of pharmacologic systems, researchers have been able to demonstrate that the active peptides in Kutapressin potentiate the action of bradykinin. Bradykinin is a vaso-active peptide generated by the blood plasma-kinin system. Plasma-kinin and its role in the inflammatory process has been a subject of great interest to researchers seeking novel anti-inflammatory drugs. A proceeding of a research symposium, published in the Federation Proceedings provides some insight into our present understanding of the effect of plasma kinins in the inflammatory process. Several investigators have independently shown the presence of bradykinin in inflamed tissues., In animal models, Kutapressin produces significant change in the capillary permeability to improve leukocyte migration. Kutapressin peptides stimulate rapid multiplication of thymocytes in tissue cultures. It drastically reduces edema induced by carageen in animals. It maintains the integrity of the cell structure as demonstrated by higher survival time of cells in the tissue culture.

Despite its wide anecdotal use by clinicians across the country, the manufacturer of Kutapressin does not intend to invest in further studies to investigate its potential use as an immune modulator at this time. As with all agents, Kutapressin does not benefit every patient, but when it works, the results can be dramatic. In fact, the objectionable need to administer it by injection is tolerated surprisingly well by children and adults when they experience pronounced improvement in their condition.

Perhaps the only significantly negative effect of Kutapressin is the possible danger of allergy. The patient must be screened against possible allergy to Kutapressin, which seems present in approximately one per cent of patients. The course of therapy I generally follow is based on original protocols by Dr's Steinbeck and Hermann; one 2cc (for adults) intramuscular injection daily for one month, then 2cc every other day for a month, followed by one injection 3x's a week for 6 - 7 months, then 2 x's a week, tapering according to patient response. The many possible variations in the use and

dosage of this drug, coupled with patient heterogeneity explain, in part, the contradictory reports of this agent's efficacy; along with the fact that as noted, this author does not feel that any one agent is the full answer to therapy at this time.

Duration of usage of Kutapressin varies widely among individuals. Unlike the first protocols by Dr. Steinback and Dr. Herman, I do not assume therapy can end at five or six months. Discontinuation of its use before the patient feels "normal/well" often results in backsliding over time. Happily, many patients in my practice have seemed to reach a state of complete recovery after usage for a year or longer (usually in combination with other therapies). Maintenance for longer periods is acceptable if indicated and helpful. Whether "cured" (a word I would use cautiously) or in a "remission" as a result of Kutapressin, the patient will generally be at a significantly improved level of functioning within a 3 - 6 month period, with some positive response expected within the first 4 - 12 weeks. Short of the drawbacks regarding allergies, Kutapressin appears to be a very safe agent, especially compared to some alternative treatments. I must strongly reemphasize, when treating any chronic condition, an agent's long term safety and efficacy is of extreme importance, in adults as well as children. This is true whether the treatment is a prescription drug, OTC, Herbal, or any other agent.

Kutapressin has seemed of particular help to patients with neurocognitive problems and/or patients with multiple viral elevated titers and an abnormal NeuroSPECT scan. Generally. Generally, this author accepts elevated viral titers as a reflection of an activated, dysregulated immune system, not necessarily or usually an acute viral infection. Kutapressin's effectiveness in children with cognitive problems is still diminished by the need to administer it by injection. Otherwise, it seems an extremely safe and frequently a very efficacious agent. In the past, I chose Kutapressin for those patients with predominantly cognitive dysfunction, not for those patients who suffered more with "fibromyalgia" symptomology, such as body aches and muscle pains. (Antedotally, low-dose, oral interferon has seemed better for these patients.)

I would readily speculate that Kutapressin, as well as other Immune Modulators, are likely to have the ability to return the body to normal. I would stress that this has generally been in the context of "combined" therapy approaches, aimed at "normalization" of the body and relief of symptoms. It has been my frustration to know for years of a number of potential new "immune-modulating" agents that are unavailable to be used because they lack appropriate evaluation and testing. Without a means of accurately sub-defining a group of CFIDS patients, and lacking an "incidence" reflecting its true frequency, pharmaceutical companies have been reluctant to invest funds for testing these new agents for this capacity. While there has been a number of "pure" agents developed, it is urgent to create a means to bring these agents into controlled tests now, not five or ten years from now.

Interferon's are produced by normally-functioning lymphocyte cells during the activation of an immune response and are part of a "cascade" of lymphokine chemical messengers. The role of interferon (IFN) alphas in the immune system and their

relationship to the other lymphokines is not completely understood. Still, there is compelling evidence of the significance of IFN-alphas in the regulation of the immune response.

Alpha interferon has been shown to have antiproliferative, antiviral and immunomodulatory activities in vitro, and in animals and humans. Recent animal studies have indicated that very low doses of oral interferon have beneficial effects in diseases induced by viruses. In calves with viral respiratory tract infections, low doses of oral human interferon alpha significantly stimulated the immune response and appetite, resulting in weight gain. In cats infected with feline leukemia virus, oral interferon treatment delayed the onset of leukemia, stimulated appetite, and significantly increased survival. Although high-dose parenteral interferon has been extensively evaluated in human patients, there are virtually no studies in humans with low-dose interferon. At high dosage, trials may be limited by side effects, many of which reflect symptoms we associate with Immune activation/CFIDS. High dosage of most of the Cytokines/Interleukins create many of the symptoms we associate with CFS/CFIDS.

I have used oral alpha-interferon antedotally in my practice. Clinically I find it more helpful for relief of muscle, bone, joint, aches and pain, but it may also aid in reaching an overall "normalization" of the body/immune system. It's mode of operation needs further understanding, as controlled trials are lacking. Still, alpha-Interferon is generally a safe and benign agent. It is given by oral drops or tablet, either of which must be kept in the mouth about 20 minutes, and is generally well tolerated. Currently, I am using a dosage equivalent to 150-200 units.

While no one knows for certain, low-dose oral interferon may be functioning by interrupting what is known as a "negative feedback loop." Assuming that the immune system is firing off inappropriately, then alpha interferon given at a very low dosage may have the ability to shut off that loop at some point. While not likely curative, low-dose oral alpha-interferon appears to be another resource to help the body feel healthier and aid a return toward "normal". It certainly seems worthy of controlled trials in the future.

Ampligen was one of the first agents used in a controlled trial of CFIDS patients. Opinions differ as to whether it is an antiviral or an immune modulator or both. Clinical improvements were obtained with Ampligen when administered intravenously twice weekly to 15 individuals who met the CDC criteria for CFS and showed evidence of encephalopathy (CFSE). Wechsler scores improved >50% in these patients. Full scale IQ increased by 12% from 106 to 119. Performance IQ increased 19% while verbal IQ increased 10%. "Viral reactivation" was reduced in 13 of 14 patients. These clinical and laboratory changes, while not judged as conclusive (perhaps a factor of the heterogenicity of patients noted above), suggest that Ampligen is a biologically active agent potentially useful in combating CFS/CFIDS. Ampligen may have the dual ability to restore immunological function and to control virus replication. Unfortunately this is a very expensive course of treatment requiring intravenous infusions. Long-term gain has yet to be proven and, as many CFS/CFIDS patients are aware, further trials with this agent remain uncertain. After initial encouraging work with this agent the

manufacturer, for a variety of reasons has hesitated continue the costly types of trials currently required by the FDA.

Along with the report of raising objectively patient IQ's and cognitive ability, many bedridden patients were able to walk and function fairly normally as a result of its use. Ampligen became the wonder drug, with a huge following eager to use it. In fact, Ampligen is both very expensive and potentially toxic, although certain newer versions are reported to be safer. Ampligen's successes and failures illustrate the problems inherent in any new medication and therapy for CFIDS. Without the "umbrella" of a scientifically validated, controlled database or other means of objectively separating patient groups, it remains this author's fear that most, if not all drug therapy trials are doomed to confusion and probable failure. As the NIH, CDC, and rest of our medical establishment come to recognize this for the "heterogeneous" mixture of patients currently represented, it remains this author's strong opinion that without the ability to sort out groups of patients (as per the initial work of Dr. Klimas's prested at the Oct. 1994, Ft. Lauderdale AACFS meeting), defining success for any given agent will remain confusing and difficult. As the patients are appropriately defined (back to the concept and necessity of a database, or other means of classification), determining which group of patients respond to which drug or type of therapeutic approach, will begin to make sense and be able to be applied clinically to appropriate patients in general.

SUMMARY

Most patients with CFS/CFIDS present with a complex series of problems. This author's approach is to reduce the condition to a series of individual pieces of a puzzle, and to then treat each one individually. This does not mitigate the need to focus on the underlying dysfunction and the source of the problem but is, rather an effective and immediate action against this devastating condition. Therefore, a patient presenting with a lot of allergies requires allergy control measures, elimination diets, and supportive medications. If yeast appears by markers or by clinical suspicion, it too should be combated in ways that are readily at our disposal. When the sleep cycle is dysfunctional, as noted earlier, often the use of low-dose Prozac, low-dose Zoloft or similar agents can provide help. My experience has shown the effectiveness of using agents that help "normalize" the body's or CNS function, rather than treating lack of sleep with sleeping medications, pain with pain medications. etc. Symptomatic thapiies may help at times or "mask" the symptoms, but do not seem to produce long term gain or improvements.

Once certain symptoms or effects can be reduced or eliminated, the introduction of Kutapressin, Interferon and "immune" or anti-viral agents deserves consideration. In general, it has been this author's experience that younger patients have the advantage of a healthier, more restorative body with more inherent body reserve, than do older sufferers or those ill for a protracted period (greater than 3-5 years). Each treatment that can help make the body healthier by stopping some of the dysfunction, increases the chances for the patient to become well, and their body to return to a healthier, physiologic state. The meaning of the term "well" may mean cured and fully functioning,

or merely improved and functioning on some type of maintenance medication. There is clinical logic in trying to help “normalize” function as much as possible, as well as minimize or stop potential long term stress and dysfunction. There are measures and medications that can help “antedotally” now, while we await the application of new medications and “controlled” trials, hopefully in the near future.

Counseling and support groups can be of great help to patients and their families. These groups should not disintegrate into “gripe sessions”. They should be a forum in which patients can discuss their condition and all of its effects. These groups should be used to exchange emerging information, function as a power base, helping to raise funds and lobby for increased research, and accelerate paths leading to therapeutic answers.

In spite of increased recognition of an immune dysregulatory state as a physical disease, underestimates (as low as 1 in 14,000, 6 or 7 per 100,000) of those affected by the CDC and NIH, indirectly slowed potential progress. Neither drug manufacturers nor Congress has been willing to fund therapeutic trials or accelerate research at appropriate levels based on these figures. Fortunately, with the reports of multiple investigators at the recent Oct. 1994, Fort Lauderdale, FL. conference showing numbers far higher than expected, there is an emerging recognition of the potential scope of this problem. Respected researchers and epidemiologists have begun citing incidences of anywhere from 1 - 1 ½% of the population. Consistent with many other clinicians, this writer would predict an occurrence rate that will most likely be as high as 3-5%, perhaps even higher. Certainly, if understand in the concept of an immune dysregulatory state, rather than the perhaps too narrow concept of CFIDS, the numbers could be aggering. We urgently need to define, address and answer epidemiological questions: How extensive is this immune dysfunction phenomenon? How do we identify it? What is its origin? Is the cause a virus, retro—virus, ozone layer depletion, toxins or something(s) as yet unidentified? What are the co-factors? Most importantly, within this context, what can be done therapeutically, both now and in the near future?

In the final analysis, research is the key factor for the eventual control of CFIDS. We cannot hope to know the safety and efficacy of agents in the immediate future unless they are monitored in controlled trials, ultimately under the umbrella of a large national clinical data base. This is similar to clinical protocols developed and used as a standard for other chronic illnesses. Any untried agent is potentially dangerous. It would seem inarguable that recognizing an epiphenomena exists and responding rapidly will ultimately be the most cost effective approach for the government, physicians, and patients. Underestimating, or frankly, ignoring this need will result in increased, long-term costs on our medical, social and business systems. Delays in research for adults were rationalized on the “belief” that this condition does not result in deaths. Sadly this ignores the huge amount of morbidity occurring in patients over time. This is NOT a “benign” disease. The loss to the minds and bodies of children who are too dysfunctional to attend school regularly is inestimable. This writer is currently working with other researchers to expedite much-needed trials. The mounting written and antedotal incidents of success using agents such as Gamma Globulin, Ampligen,

Kutapressin, and Interferon give cause for sincere optimism in treating CFIDS patients. But research must be funded to find more agents and determine how they work in carefully controlled studies.

With the presentation of information at the Ft. Lauderdale conference, it is this author's firm feeling that there are no questions regarding the reality of the problem. The difficulty ahead is to find the scientific answers and explanations for this "new" phenome