

# **It Is What It Is: Searching for Truth**

National CFIDS Foundation

Medical Committee

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It has often been said that "To have wisdom means to have more questions than answers." When simply applied to the field of Chronic Fatigue Syndrome (CFIDS/ME), there are certainly many more questions than answers generally speaking. However, for the National CFIDS Foundation (NCF) to run out of questions would imply that we have given up on learning about this disease and that definitely would be neither wise nor prudent, especially for the worldwide patient community whom we represent.

In this important essay, the NCF examines and reports on keynote discrepancies between medical observations made during the time period of the Lake Tahoe outbreak (1984 - 1986) and what was published in the *Annals of Internal Medicine* journal article (1992) on the Tahoe outbreak itself. One discrepancy is further highlighted and exacerbated by recently published research (2006) that not only confirms the initial Tahoe observations but expands on them as well. The NCF questions the rationale as to why the early medical test results failed to make it to the *Annals* article and ultimately to the general patient population. The NCF's research is discussed within the context of these scientific observations.

## **Initial Observations: 1985 - Incline Village, Nevada**

As part of the NCF's overall efforts, the Foundation contacted **Hillary Johnson**, author of *Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic* to inquire directly about one particular passage, found on pages 90 - 95, from her book. Because of its importance, Ms. Johnson has granted the NCF exclusive permission to use these pages as part of this essay. These book pages will be made available on our website for patients to read. The NCF greatly appreciates Ms. Johnson's cooperation to share this brilliant excerpt from her acclaimed book. The information herein comes from an interview with **Susan Wormsley** by author Hillary Johnson [1].

Johnson began by commenting about physicians **Paul Cheney**, M.D., Ph.D. and **Daniel Peterson**, M.D. in Incline Village. "Starting that fall, Peterson and Cheney began to observe an outbreak of rare immune system cancers not only among people who were ill with the epidemic disease but among other previously well residents of Lake Tahoe's north shore."

One such case was that of an attorney who was Peterson's patient who had a tumor at his jawline. Peterson sent the attorney to Stanford University's medical center where a senior pathologist had studied the tumor cells and determined that the diagnosis was "undifferentiated B-cell lymphoma." The tumor site was the parotid or salivary gland. (The NCF had previously reported that rubulaviruses were known to directly infect the parotid glands.)

Later, a plumber and handyman and Cheney patient had come to the clinic with a tumor on his neck. This tumor was also in the parotid gland and was characterized by Stanford as a "mixed salivary adenoma." This apparently was the tip of the iceberg since Cheney and Peterson had seen additional patients with mixed salivary adenomas and others who had been diagnosed with B-cell lymphomas.

According to Johnson, "Cheney, in particular, began to mull the likelihood of spotting lymphomas at a presymptomatic stage." He ultimately met up with **Susan Wormsley**, a flow cytometry expert on the west coast. "Flow cytometry is an expensive, rarefied technology for quantifying and qualifying immune system cells; this technology is used to diagnose and stage the severity of lymphomas." Wormsley devoted much of her time to evaluating very early B-cell lymphomas.

Johnson continued, "Not long after establishing Cytometrics, Wormsley had begun to take advantage of one of the technology's most significant applications: monitoring the progression of B-cell lymphomas. In 1976 three Harvard scientists had developed the test, which was a highly sensitive method of finding monoclonal, or cancerous, B-cells in the blood. Called the kappa/lambda clonal excess assay, the test was able to detect lymphoma cells even when they were present in extremely low numbers." (It should be noted that the NCF had previously identified many patients who tested positive by the kappa/lambda assay. The kappa/lambda assay has often been used as an assessment tool for suspected multiple myeloma or bone cancer. Patients who tested positive did participate in additional cancer tests from those oncologists who were involved with these patients.) "After studying samples from approximately fifty patients, Wormsley estimated that the rate of clonal excess abnormality in the fatigue patients from Nevada was at least 25 percent."

Wormsley stated, "Actually there were several abnormalities that we saw in these patients." One was a voluminous amount of cell debris. She continued, "Right from the time we separated and stained the cells, we saw a lot of debris...Just broken-apart cells, pieces of cells and platelets. And we don't see that in anything else that gets sent to us." (The NCF suspects that this debris represented either cellular apoptosis or necrosis.) However, one of the most noteworthy observations that Wormsley herself made pertained to B-cells:

Wormsley commented, "Right from the beginning, these people seemed to have extremely low percentages [of B-cells], sometimes only one percent or two percent of their white blood cell population instead of the eight to twelve percent that we normally see....three of the first five Tahoe patients tested had no B-cells at all, a finding that was repeated on additional tests." Not only did Cheney's patients suffer from a B-cell deficiency but several of these patients produced abnormally low levels of several classes of immunoglobulins as well.

Johnson stated, "One of the most striking immunological aberrations Wormsley observed, however, was abnormal ratios of T-cell subsets. T-cells are a major category of immune system cell; they regulate production of disease-fighting antibodies. Two primary T-cell subsets are "helper and suppressor" T-cells, which boost and suppress antibody production, respectively.

In AIDS the normal ratio tends to be dramatically skewed in favor of suppressors. Since this finding is virtually diagnostic of AIDS, Cheney and Peterson were curious to know the T-cell subset profile in the Tahoe malady.... Wormsley's result showed that four of five Tahoe patients did have abnormal helper-suppressor ratios. But, unlike the ratios in AIDS sufferers, they were low in the numbers of suppressor cells. Instead of one-to-two or one-to-three, which are typical of healthy people, the Incline patients had helper-suppressor ratios of five-to-one, ten-to-one, and higher. It was the mirror image of AIDS."

According to Johnson, "Cheney and Peterson decided to run all five samples again; the results were identical. Then they expanded the test to include more people. Approximately half of the twenty additional patients were found to have abnormally low ratios of suppressor cells to helper cells. When they searched the medical literature for other diseases that produced similar inverse ratios of T-cells, they discovered that the finding had not been reported before. Researchers had observed elevated ratios in certain autoimmune diseases such as multiple sclerosis and lupus, but always the elevation was due to an increase in the helper cell population, as in AIDS, rather than a decrease in suppressors."

The NCF walked away with the following notes from this excerpt from the book. First of all, this information came from Susan Wormsley, the flow cytometry technician. Next came the medical observation that CFS patients tested positive on the kappa/lambda assay. This is a significant finding because kappa/lambda light chains are the direct result of abnormalities within the bone marrow B-cell lineage. Likewise, the inherent lack of B-cells in Cheney and Peterson's Tahoe patients **raises a big red flag** since this is reflective of a serious problem with humoral immunity. As **Nancy Klimas**, M.D. previously stated "CFS is a form of acquired immunodeficiency" may ultimately turn out to be the best description for this disease [2].

### **The Discrepancy: 1992 Annal of Internal Medicine - Truth, Deception or Sanitization?**

Most of us, in our youth, were told to always tell the truth. This is part of life's 'Golden Rules.' Another rule is that omission is not truth nor is it truthful. In fact, omission isn't even a variation of the truth. What does the NCF's Medical Committee mean by this?

To fully appreciate the problem here, let's reference the infamous 1992 Tahoe outbreak paper titled *A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection* [3]. The authors included names such as Buchwald, Cheney, Peterson, Henry, Wormsley, Geiger, Ablashi, Salahuddin, Saxinger, Biddle, Kikinis, Jolesz, Folks, Balachandran, Peter, Gallo and Komaroff.

In their study of 259 patients, of whom 29% of these patients were either bedridden or shut-in, several results were noted. These included a higher mean CD4/CD8 ratio, the presence of punctate areas consistent with edema or demyelination and active HHV-6 replication in significant numbers of patients. Lymphocyte counts were determined by flow cytometry and the authors reported that "No significant differences were noted in the total T-cell or B-cell number."

So therefore, given the reported observations in Osler's Web regarding the lack of B-cells along with kappa/lambda assay positivity, the NCF questions the 1992 Tahoe paper. Was this paper sanitized in such a way so that these abnormalities weren't reported? Were these abnormal patients excluded from the research study that was reported in this medical journal article? At least three people were fully aware of the flow cytometry test results for the Tahoe patients according to *Osler's Web*. These included Peterson, Cheney and Wormsley. However, all three names were also listed as authors in the 1992 *Annals of Internal Medicine* journal article. Why was this serious B-cell deficiency and kappa/lambda positivity ignored and furthermore, why didn't Cheney or Peterson make this a focal point for medical arguments that were made about this disease? To discover that "three of the first five Tahoe patients tested had no B-cells at all" seems a fairly cut and dried scientific argument that leaves very little wiggle room for interpretation. Since the CDC reviewed their patient records, how could the agency miss something that is as obvious as well as critically important? As for the HHV-6 connection, research completed at the Infectious Diseases Department at Mayo Clinic has shown that selective reactivation of Human Herpesvirus-6 Variant-A occurs in critically ill hosts [4]. This may help to explain why this virus is frequently found in patients with CFS.

### **Fast Forward: Latest Research Confirms a Severe B-Cell Immunodeficiency in CFS Patients**

An important European medical journal article was recently published by a team of researchers from Minnesota. These scientists had identified a critical defect in CFS patients [5]. The NCF will post this article on its webpage for patients to read.

**Fatih Uckun, M.D., Ph.D.** is one of the researchers who was involved in this study. Dr. Uckun's specialization is oncology, hematology and bone marrow transplantation. He stepped down last year as a 14-year editor for the international medical journal *Leukemia and Lymphoma*. Dr. Uckun was a former professor at the University of Minnesota Medical School. He was a Stohlman Scholar of the Leukemia Society of America and has published extensively with over 425 peer-reviewed medical journal articles in the oncology field.

Dr. Uckun, along with his colleagues, recently published a paper titled *Clinical activity of folinic acid in patients with Chronic Fatigue Syndrome*. In this article, the authors had found that 94% of the 58 CFS patients evaluated had a B-cell immunodeficiency with a marked depletion of their CD19+IgM+ mature B-lymphocyte population. The CD19+IgM+ cells ranged from a low of 0.5% to a high of 53%. These researchers concluded that there was "a high incidence of severe B-cell immunodeficiency" in the CFS patients.

As a possible treatment, the research team utilized the drug Leucovorin, a folinic acid derivative, in doses that ranged from 75mg to 100mg per day for several months. The research team found that 81% of the CFS patients reported significant subjective improvement with increased energy level and reduced pain within two months. In addition, no patient reported severe side effects from Leucovorin treatment. Unfortunately, the research team failed to perform patient flow cytometry measurements upon completion of their drug trial [6]. This would have

allowed the scientists to gain additional insight as to whether Leucovorin treatment positively affected and improved CD19 B-cell parameters. This research does, however, provide important treatment clues.

According to flow cytometry results, CD19 B-cell counts typically range from approximately 10% to 20% depending upon the reference lab used. From the NCF's own studies, we identified CFS patients who had low CD19 B-cell counts of 3% to high CD19 counts of 66%. This is of interest because CD19 B-cells play an important role in clinical oncology [7,8]. CD19 expression is induced at a point of B-cell lineage commitment during the differentiation of the hematopoietic stem cell and its expression continues through various cell stages to mature cells. CD19 B-cells have been found to be useful in the diagnosis of lymphomas since some B-cell non-Hodgkin's lymphoma (NHL) subtypes are considered to be malignant counterparts of distinctive steps in normal B-cell development [9].

However, Dr. Uckun's research allows for additional insight to be applied to this study. One observation is that a B-cell immunodeficiency characterized by a marked depletion of CD19+IgM+ mature B-lymphocyte population is associated with a condition known as Common Variable Immunodeficiency or CVID [10]. Since there are inadequate numbers of circulating CD19 B-cells in the peripheral blood, this represents a hypogammaglobulinemic condition due to the reduction in circulating serum immunoglobulins [11]. This is a serious impairment of the humoral immune system. As such, one of the treatments for CVID is intravenous immunoglobulins or IVIG [12]. Interestingly, one reported treatment for CFS has been the use of IVIG [13]. On the other end of the CD19 scale, aberrant production of CD19 B-cells can represent a proliferative phase of cancer or NHL. Ultimately, two B-cell phases may be associated with this disease. The first is best represented by CVID as mature peripheral CD19 B-cells diminish over time due to alterations to the progenitor B-cell lineage in the bone marrow. Then, should malignant transformations take place to alter the B-cell progenitors, these mature CD19 B-cells accelerate in number and represent a proliferative response associated with cancer. The NCF does believe that given what we currently know, CFS may be associated with a proliferative B-cell process that disregulates T-cells in such a manner to ultimately predispose patients to cancer or to indolent forms of lymphoma.

The NCF's comments are in agreement with the previous research reports stating that the "results demonstrate that the presence and amount of p53 protein fragmentation directly correlates with the presence and amount of low molecular weight RNaseL fragments in PBMC samples. These data indicate that native p53 protein is fragmented at a later point in the disease cycle than RNaseL protein. The loss of functional p53 protein in PBMCs render these cells unable to respond to normal growth inhibitory stimuli and provide the means whereby unregulated cell growth occurs, ultimately giving rise to hematopoietic tumors [14]" and that persistent inactivation of the p53 protein may lead to an increased incidence of cancer [15].

### **NCF's Research Background: Stat-1, PIV-5, and CD19....Putting the Pieces Together**

The NCF was the first patient group to recognize and embrace the critically important role of the Stat-1 protein in patients with this disease. By directly funding our own research on Stat-1

[16], we were able to verify the discoveries previously made by other scientists in the field [17,18,19,20]. Stat-1 is responsible for the maintenance of the host's innate immunity [21] and its loss results in lethal viral disease [22]. In fact, by interacting directly with interferons, Stat-1 provides key host defense against both viral and bacterial pathogens.

Since new scientific discoveries generally build upon those previously made, this is the direction of research funded by the NCF. Once the Stat-1 research was underway, the NCF made a profound effort for its "proof of concept" theory that Parainfluenza Virus-5 (PIV-5), a rubulavirus, could be involved in this disease [23,24] due to the scientific fact that Stat-1 is a direct and destructive targeted result of PIV-5 infection [25,26]. During this same time period, the NCF became aware of the discovery for "Cryptovirus," a term coined by its discoverer [27]. This virus, a rubulavirus and member of the Parainfluenza Virus-5 family [28], was identified in patients with CFS.

Interlaced with these scientific discoveries was an additional fact that the fusion protein for "Cryptovirus" [29] matched that for the SER strain of PIV-5 [30], a porcine strain that had been previously identified in swine herds with Porcine Respiratory and Reproductive Syndrome (PRRS) [31,32] suggesting a potentially vital epidemiologic link between the two and thereby establishing the source of the originating virus.

Previous research [33] suggested an important regulatory link between the Stat-1 protein and CD19 mature bone marrow B-cells that serve to play a critical role in humoral immunity. CD19 B-cells act as a positive modulator or regulator of Stat-1 activation. This is important because the NCF's research study on Stat-1 levels in CFS patients yielded two basic group abnormalities; one with abnormally low levels of Stat-1 and another with very high levels of Stat-1. While Stat-1 deficiency has been associated with impaired NK (natural killer) cell function as well as the inability to reject tumors [34], high activation levels of Stat-1 have been associated with cancer [35]. Furthermore, the NCF had patient research data that further supported the basic vital link between Stat-1 levels and CD19 B-cell counts. In fact, those patients who had abnormally high Stat-1 levels also had higher CD19 counts that had been confirmed by flow cytometry. As mentioned in this article, high CD19 B-cell counts have been associated with NHL [7,8], a disease in which malignant cancer cells are found in the lymphatic system. This is important because NHL and brain cancer had previously been reported to be increased in patients associated with the Tahoe outbreak [36]. Since CD19 B-cells regulate Stat-1 activation, it is a logical hypothesis that leads the NCF to the premise that the bone marrow is directly involved in the disease pathophysiology of CFS. This insight has been pathologically confirmed by those patients who have undergone bone marrow biopsies and who have also taken part in the NCF's ongoing research studies. Furthermore, Dr. Uckun's paper reaffirms the NCF's findings of abnormal CD19 B-cell counts associated with alterations in Stat-1.

It is poignant to emphasize the fact that PIV-5 can directly infect bone marrow B-cells [28]. The authors of this paper suggest that if PIV-5 establishes persistent infections in a reasonable proportion of individuals, then it may be timely to re-evaluate the role of PIV-5 and other paramyxoviruses in chronic human disease especially since there are tools to perform such studies more incisively. Furthermore, these scientists also comment that since PIV-5 and other

paramyxoviruses interfere with cellular processes, including the interferon response, and if there is a loss of cellular function in cells that are persistently infected with paramyxoviruses, the rationale behind any possible link with disease becomes easier to make. The NCF acknowledges that our research funding on Stat-1 levels in CFS patients provides direct in-vivo confirmation for this loss of cellular function attributable to PIV-5 infection. This also provides an informative view into the important role of CD19 B-cells in the pathogenesis of chronic PIV-5 infection and ultimately, CFS pathology.

The NCF Medical Committee's conclusion is that the bone marrow must become the main focal point for research studies if we are to make serious in-roads into potential drug treatments for this disease. To ignore these basic facts is akin to putting your head in the sand. To ignore proven science would be detrimental to the patient community. This problem is not going to disappear. The bone marrow represents the ground zero point of impact in this disease as characterized by the virus identified, the supportive cellular findings as well as confirmations from various research based pathology tests done on patients to date. This is where the road leads us. To fund any research grant proposals that are looking at mechanisms of the disease instead of establishing the basic science that initiates them will not lead to any therapeutic advances for those suffering from CFS (CFIDS/ME). To find future answers, we must continue to follow the road less traveled.

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